S. HRG. 100-821

AIDS TREATMENT RESEARCH AND APPROVAL

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

ONE HUNDREDTH CONGRESS

SECOND SESSION

ON

EXAMINING WHAT PROGRESS HAS BEEN MADE, WHAT IS NEEDED TO MAKE PROGRESS MORE RAPID, AND WHAT BARRIERS STAND IN THE WAY OF BETTER RESEARCH AND SWIFTER DISTRIBUTION OF HOPEFUL THERAPIES

JULY 13, 1988

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AIDS TREATMENT RESEARCH AND APPROVAL

WEDNESDAY, JULY 13, 1988

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, DC.

The committee met, pursuant to notice, at 9:20 a.m., in Room SD-430, Dirksen Senate Office Building, Senator Edward Kennedy (chairman) presiding.

Present: Senators Kennedy, Pell, Simon, Mikulski, Stafford, and Weicker.

Also present: Senator Cranston.

OPENING STATEMENT OF SENATOR KENNEDY

The CHAIRMAN. We will come to order.

We will have a full morning. We will have interruptions by votes, so we are going to move along as rapidly as we can.

We will ask our witnesses, as well as the Senators, to be as brief as possible but as complete as possible in terms of this important hearing.

This morning the Committee on Labor and Human Resources continues its work on the AIDS crisis. Much has happened since our last public inquiry into this crisis. The committee has unanimously reported, and the Senate passed, legislation to require a comprehensive response to the AIDS crisis in the areas of treatment, research and education.

The President's AIDS Commission has completed an impressive and comprehensive report on the Federal Government's duties, if we are to defeat this scourge.

After more than a year's delay, responsible medical authorities in the Administration have prevailed over those who tried to block and delay the national mailing on AIDS.

And in the time since our last hearing on this topic, thousands more Americans have died of AIDS. In the time since our last public hearing, scientists have confirmed what we have long feared; that virtually all of those who are infected with the AIDS virus, will eventually contract and die of AIDS.

What this means is that our previous estimates of the cost of AIDS to the nation have been underestimated by at least a half. There are those who say that the alarms have stopped on AIDS; that the level of concern can now level off, because the disease has done so.

I respond that the crisis just doubled on us while many sat back ready to settle in to a deadly "business as usual."

History will long marvel at the Americans of the 1980s who allowed a virus that cares nothing for our moral preferences to invade our society almost unchecked when we knew better.

It will marvel that we knew our enemy, and it is the virus and not the victims, but wasted precious years and countless lives blaming the sick for their illness.

They will marvel that we already had a workable vaccine, an honest education, but that we allowed children to die while we debated whether or not to tell them the truth.

Society can say with near certainty what the virus plans to do for the next ten years. But there is little certainty what our own government plans to do about it.

We already know volumes about what the government has not done. Admiral Watkins, who joins us this morning, has reported that the Federal Government has not yet established a unified, comprehensive policy in response to AIDS.

And he has written that many of the decisions about the Federal response to the HIV epidemic appear to have been made on the basis of criteria other than medical and scientific data about the needs of persons with HIV infection or AIDS or future projections about the epidemic.

The Chairman of the President's AIDS Commission concluded that the Commission is deeply concerned about the Federal Government's slow response to the HIV epidemic.

This Committee is also deeply concerned. We do not yet have a national response to AIDS. We have a system of sporadic lip service when the crisis calls for committed leadership.

We do not yet have a cure for AIDS, and we do not yet know what molecules will deliver us from this scourge. But we do know that those molecules, when they are found, will be discovered by the strongest forces known to science and mankind: vision, commitment and leadership.

Without those ingredients, the search for a vaccine and cure will be inexcusably delayed; far too many more will die.

We will hear today from two other members of the joint chiefs in the war on AIDS, Commissioner Frank Young of the FDA and the scientist in charge of the AIDS research effort at the National Institutes of Health, Dr. Anthony Fauci.

We expect to hear what progress has been made, what is needed to make progress more rapidly, what barriers stand in the way of better research and swifter distribution of hopeful therapies.

The President's AIDS commission has made a comprehensive series of recommendations to the country which would expand and assure a national commitment to defeat this virus.

The President has taken those recommendations under advisement for 30 days. These recommendations are overwhelmingly sensible, and I hope the President will heed the voices of science and reason in reviewing them and making his decision.

It is nearly two years since the National Academy of Science has recommended that the President's AIDS Commission be created. The Nation's graveyards are filling with those who waited desperately while the government sat patiently on its hands.

We know enough to act. The time for waiting is past.

At this point we will receive for the record a statement by Senator Hatch.

[The prepared statement of Senator Hatch follows:]

Statement by Orrin Hatch

Hearing on AIDS Treatment Research and Approval

July 13, 1988

Mr. Chairman, I am pleased that you are holding this hearing today--a hearing that will focus on this country's efforts to provide the best treatment available to those infected with the AIDS virus.

There have been over 60,000 people diagnosed with AIDS in this country since June of 1981 and over half have died. Almost every one either knows someone with AIDS or knows someone who has a friend afflicted with the dread disease.

The members of this Committee have made a commitment to do something about AIDS. We have passed legislation to authorize substantial levels of funds for programs in the Public Health Service--programs for research, training, services for AIDS patients, and public education. These efforts demonstrate the commitment of the members of the Committee and the Senate to fight the battle against AIDS.

Today, we will hear from Admiral James Watkins, Chairman of the Presidential Commission on the Human Immunodeficiency Virus Epidemic and Dr. Frank Young, Commissioner of the Food and Drug Administration.

While I do not agree with everything in the Commission's report, I want to acknowledge the contribution that Admiral Watkins and the members of the Commission have made to help us better understand the AIDS epidemic. Admiral Watkins, you noted in your letter to the

President, "issues surrounding the HIV is exemplified by the nearly daily development of scientific information about the virus which will continue to demand frequent review by officials in the public and private sector." I agree that the epidemic demands that we remain flexible in addressing the public health and public policy issues.

Dr. Young is the Commissoner of the Food and Drug Administration. The FDA is celebrating its golden anniversary this year--fifty years of protecting the American public by regulating food, drugs, medical devices, and cosmetics. The efforts that the FDA has made over the years to protect our health, while supporting the development of new drugs and medical devices, is a matter of record. The treatment INDs are a major step towards bringing new drugs to those with AIDS in a timely manner. I am sure Dr. Young will discuss how this is being implemented by the FDA. The medical profession and the public have come to expect that drugs receiving the approval of the FDA are both safe and effective.

I would like to express my thanks to Dr. Young for the effort that has been made by the FDA to walk the very thin line of quickly moving new drugs through the approval process while continuing to protect the public from unproven drugs and devices. I know that there are times when the FDA's critics complain about how long it takes to complete clinical trials, but there is a need for solid data showing the safety and effectiveness of new drugs.

I look forward to reviewing the recommendations of today's witnesses, as part of this Committee's ongoing effort to provide the Public Health Service with the tools it needs to continue to combat this epidemic.

The CHAIRMAN. I would recognize the Senator from Rhode Island.

OPENING STATEMENT OF SENATOR PELL

Senator PELL. Thank you very much, Mr. Chairman. And I congratulate on holding this hearing, and I congratulate Admiral Watkins on his excellent and the work he has done in taking what seemed an impossible job and pulling the threads together and giving us some hope that some help may be found.

And I would add that I think research into the treatment of AIDS, research into the promising drugs to treat it, is crucial.

Each day we learn more and more about AIDS. Each day we hope a cure will be found. But today, all we know is that AIDS kills, and there's no known cure or perfect treatment.

And under these circumstances, we have a special obligation to do all that we can to ease the suffering of the dying and give those afflicted the best possible chance to live.

I apologize for not staying here for the hearing, but I am presiding over the foreign relations committee that is starting just about now.

Thank you very much, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Pell.

Senator Simon?

OPENING STATEMENT OF SENATOR SIMON

Senator SIMON. Thank you, Mr. Chairman. I want to join in commending you for holding the hearing. And I regret that I serve on that foreign relations committee, and we have a very mean tough chairman there who is just leaving, and I am going to have to get over there.

Just a couple of points here. One is, I want to join in commending Admiral Watkins for the leadership he has provided. Frankly, I think most of felt that commission that was put together wasn't going to do anything constructive. And you ended up just really doing a job that I think this Nation can be very, very proud of.

Two points that I hope, if I don't get back here, Mr. Chairman, I hope will be brought up. One is, the whole question of accurate funding for testing centers. In some areas we still have a wait for those who think they may have AIDS. And that waiting period is dynamite.

People who know they have AIDS, with rare exceptions, do not spread it. But people who are uncertain can be spreaders of the disease.

And the second is what level of research should we be providing? I know this is not an appropriations committee, but at least a little informal information my office has received is that we could be using about $100 million more than is being appropriated from the appropriations committees right now that will be pending very shortly before the Senate.

I think we ought to be looking at what level of research money can we effectively use, and our failure to provide the money that is needed may save a few dollars today but is going to cost us both in dollars and in human misery in the long, long term.

But again, I'm going to stay for a little while, and I hope to get back as soon as I can. But I think that these are very important hearings, and I commend you for holding them.

The CHAIRMAN. We want to thank you, Senator Simon and Senator Pell. Both have been enormously supportive of the research, education, and treatment programs.

And we look forward to their continued participation.

We are aware of your other hearings, so we hope you will be able to get back with us. And thank you very much for your presence here.

Senator Mikulski, we welcome the Senator from Maryland.

OPENING STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Thank you very much, Mr. Chairman. And thank you for organizing this oversight hearing on the status of AIDS.

I know that we have a distinguished panel and group of witnesses. But I did a little bit of my own oversight over the last couple of weeks, in which, in my own city of Baltimore, which has a significant AIDS population, I met with people who have AIDS. I met with families who love them and are trying to support them through this crisis.

I met with scientists at Johns Hopkins, both those who are trying to find a cure and those who are trying to do innovative patient services.

And then I met with the nonprofit groups out there on the frontier, trying to find innovative ways to provide services. In that process, I saw people who held the test tubes in which they hope to find a cure, and also held the hands of those who were dying.

Mr. Chairman, what I saw from my visits is that what we are doing is quite significant, but that we need to focus our attention on several things.

One, finding the cure and treatment for AIDS. But also, we need to be able to develop the educational programs to contain the spread of further infection, and also, contain the spread of fear.

And last, but not at all least, while we are looking for the high tech solutions for finding the cure, we have to be able to fund the high-touch care that's needed to deal with those people who already have AIDS.

Just to summarize: we need access and eligibility for health care. Adequate treatment facilities, both home care and home health care; and freedom of discrimination.

Mr. Chairman, I have an article from the Baltimore Sun today that I would like to put into the record. It is about a six-year-old little girl who died of AIDS. She spent her first 3½ years at Francis Scott Key, a facility of Johns Hopkins, because nobody would take her, but it was the nurses there who loved her.

Finally a nurse took her home into her family where they adopted her; excuse me, they took her as a foster child. They wanted to adopt her, but they didn't adopt her because in foster care, her enormous medical needs would at least be paid for.

And last, but not at all least, this gallant six-year-old girl died only to face discrimination from the funeral home industry who wanted to charge a far higher fee.

Finally there was a Catholic funeral director who, moved by compassion and his own sense of values, saw this.

This story is so telling of what is faced in the AIDS community, Mr. Chairman, I ask unanimous consent that that story, the story of Kedra, be told to this Congress and to all Americans who will read it.

I ask unanimous consent that that be placed in the record.

The CHAIRMAN. Without objection it is so ordered.

[The article referred to follows:]

Little girl born with AIDS never really had a chance

Kedra Corey, born to a drug abuser who had AIDS, became the foster child of a Middle River couple with whom she lived more than two years.

Services

Viewing for Kedra Corey will be from 3 to 5 p.m. and 7 to 9 p.m. today and tomorrow at Charles S. Zeller & Son funeral home, 6224 Eastern Ave. The funeral will be at 11 a.m. Friday with burial in Oaklawn Cemetery, 7225 Eastern Ave. The Rev. Melvin Tuggle will conduct the service.

Baltimore
The Sun
7/13/88

By Randi Henderson

Kedra Corey died Monday afternoon in the arms of the man she called Daddy. She would have been 6 years old on July 26, a little girl who never had a chance at a full and productive life but nevertheless beat the odds in surviving as long as she did.

Kedra died of complications related to AIDS. Born at City Hospitals (now Francis Scott Key Medical Center) to a woman who used intravenous drugs and had AIDS, she lived the first 3½ years of her life in the hospital. Her mother died when she was 2. Since March 17, 1986, she had been in permanent foster care in the Middle River home of Emery and Lee Corey.

Mrs. Corey, now retired, was a unit clerk in the pediatrics ward of the hospital. She and her husband got to know and love Kedra and became convinced that a hospital was no place for a child to grow up. They took custody as foster rather than adoptive parents so that the state would continue to pay for Kedra's medical expenses, which were considerable.

Last fall Kedra, who attended kindergarten at Hawthorne Elementary School, was the subject of a profile in *The Sun*. Her name and the names of the Coreys were not used because the family feared discrimination at home and at school. At school the principal and staff were aware that Kedra had AIDS, but other children and their parents did not know of her illness.

Now, Mrs. Corey feels, there is no longer any reason to conceal the family's identity. "There's no more suffering for Kedra," she said, her grief tinged with bitterness. "No more doors slammed in her face, no more discrimination. Now I can speak up for all the others who have to face what we faced."

The last battle the Coreys fought for Kedra was over funeral arrangements. Kedra had been healthy and active for the first two years she was with the Coreys, but in May her health began to decline and the family began looking for a funeral home that would provide the kind of services they wanted.

"I wanted her embalmed and in an open casket," Mrs. Corey said, but when she began calling funeral homes in the Essex/Middle River area she found that most would not embalm a person with AIDS and those that would charged several hundred dollars above their usual fees because of special equipment needed to avoid contact with AIDS-infected body fluids.

After frustrating hours on the telephone, the Coreys finally arranged for Kedra to be buried by Charles S. Zeller & Son. The casket will be open and the mortician did not charge extra for embalming, Mrs. Corey said. The Rev. Melvin Tuggle, who was a chaplain at City Hospitals when Kedra was there and became very close to her, will conduct the funeral service Friday.

Kedra's health was remarkably stable in her years with the Coreys and until May she even managed to escape the colds and other minor illnesses that go through a family. She lived in the modest two-story house with Mr. and Mrs. Corey, who are both in their late 50s and had already raised five children of their own to adulthood; Mr. Corey's elderly mother; the two youngest Corey children, and Bo, her beloved English spaniel. Few in the neighborhood knew the details of the family situation, although some may have noted the oddity of a black child in a white family. "They probably just think we babysit her," Mr. Corey once said of his neighbors.

In May Kedra was hospitalized at Johns Hopkins Hospital when wounds in her mouth from dental work began to bleed uncontrollably. She had hepatitis and her liver was failing, doctors found, but after a week her condition began to improve enough so that she could go home. But the family knew that Kedra's disease had finally caught up with her. "We knew it was a matter of time," Mrs. Corey said. "We knew it wouldn't get better, it would get worse."

Miraculously — a term that the Coreys use cautiously — Kedra perked up during the ensuing weeks. A huge scab on her lip that doctors were afraid would cause hemorrhaging if it became dislodged dropped off one night with no bleeding and didn't even leave a scar. It happened just after a visit from Mr. Tuggle. "We're not real strong religious people," Mrs. Corey said at the time, "but I do feel there was another presence in this house that night. You just don't have big open sores suddenly heal."

The rebound continued until about two weeks ago when Kedra's health once again took a downward turn. In her last days she was "very weak and very tired, but in no pain," Mrs. Corey said, and Kedra was not hospitalized again. She was conscious until the end.

On Monday afternoon Kedra was lying on the couch in the living room, where she had been spending her days, and raised her head up. Mr. Corey, thinking she was going to cough, put his arm behind her head and she reached out for him. "She laid her head back," Mrs. Corey said, "and that was it."

The CHAIRMAN. Senator Stafford.

OPENING STATEMENT OF SENATOR STAFFORD

Senator STAFFORD. Mr. Chairman, first of all I would like to take this opportunity to congratulate Admiral Watkins on the excellent job he and the other members of the Presidential Commission on the HIV Infection have done and their efforts are reflected in their report.

Today, these witnesses will discuss the activities involved in the research and approval process for AIDS treatemnt. The need for the development of new medicines to treat this disease is urgent. According to statistics by the Center for Disease Control, in the past 2 months over 4,000 men and over 400 women have been diagnosed with AIDS. Of this number over 700 men and 227 women are IV drug abusers attesting to the fact that this population is seeing a significant increase in the number of AIDS cases. Unfortunately, if any of these women are pregnant or become pregnant their children, the innocent victims, will be born not only drug addicted but possibly with the disease.

There is so far only one drug available for the specific treatment of AIDS and it is very costly. Other drugs are in the pipeline but for people with AIDS their time is running out. Waiting years for these drugs to go through the final approval process is deadly for these individuals. I hope this hearing today will provide us with information and some solutions to the problems I have been hearing relative to the development and approval process for AIDS treatment.

The CHAIRMAN. We welcome the Senator from California, Senator Cranston, former member of this committee, who has been tireless in his leadership on this issue. He has been enormously supportive of all the legislation that has come out of our committee in the areas of research and treatment and training, as well as the anti-discriminatory provisions and testing provisions.

He has been one of the really outstanding leaders on this issue in the Senate, as well as a good friend to all of us, and has developed a very special understanding and knowledge about this issue.

We look forward to his testimony. We welcome you.

STATEMENT OF HON. ALAN CRANSTON, A U.S. SENATOR FROM THE STATE OF CALIFORNIA

Senator CRANSTON. Thank you very much, Senator Kennedy. I appreciate those very generous words. And I applaud all your good works on this front, and on so many others.

I deeply appreciate the opportunity this morning to share briefly with you my great interest and concerns regarding the research and development process for new therapies to treat AIDS.

I applaud the Chairman of this committee and the other Members of the Labor and Human Resources Committee for your leadership on the AIDS issue, leadership which unfortunately has been lacking from the White House.

Your efforts in particular to expedite the development and approval of new treatments for AIDS through S. 1220 and this hearing today are deeply appreciated by so many Californians and

people throughout the country who have been infected with the HIV.

I asked to testify before the Committee today because there have been numerous concerns expressed to me by my constituents that the government-run and government-regulated clinical trials are not open to all experimental therapies, or to all individuals with AIDS, on an equal basis.

Although millions of dollars are spent annually on drug development and clinical trials, many people with AIDS are still experiencing difficulties in gaining access to experimental treatments.

Recent reports from both the Presidential Commission on the Human Immunodeficiency Virus Epidemic and the National Academy of Sciences found that women, minorities, hemophiliacs, drug users, and children have had only limited access to clinical trials.

Much more outreach is needed to ensure that all individuals can participate.

In addition, concerns have been expressed to me that less conventional experimental treatments are not being tested with the same vigor, interest and speed as is, for example, AZT. Numerous promising experimental drugs have taken one year or longer to get into trials.

We have heard explanations—lack of resources, lack of staff—for those delays. But explanations and excuses do not provide comfort or hope to people who are dying.

Because I was deeply concerned about this problem, I offered an amendment that was enacted as part of the Fiscal Year 1988 Labor-HHS appropriations act, to require the NIH to take all possible steps to ensure that all experimental drugs for the treatment of AIDS that have shown some effectiveness are tested in clinical trials as expeditiously as possible, and with as many subjects as are scientifically acceptable.

I am very pleased that this provision has again been included in the Fiscal Year 1989 Labor-HHS appropriations bill now moving through the Congress.

Mr. Chairman, as you know, there are about 30,000 Americans with AIDS alive today. Tens of thousands more have symptoms resulting from the HIV infection. And countless thousands of others are infected with the HIV but have yet to show signs of disease.

As all the recent projections indicate, those numbers will continue to rise over the next few years until in 1992, when there will be nearly a quarter of a million people with AIDS. And of course, that is not the end of it all.

With only one approved AIDS drug, there are far more individuals interested in participating in clinical trials than there are slots for them.

People want to enroll in clinical trials, both for their own sakes and for the sake of gaining information that may help find new treatments for others with the HIV infection.

Lack of access to approved trials is part of what drives many individuals to try underground experimental remedies.

As you well know, out of desperation, people with AIDS will try virtually any drug or any treatment that they believe has a chance, no matter how slim, of succeeding. There are entire networks in California, New York, and elsewhere, for buying and dis-

tributing such treatments, most of which are not being tested in controlled clinical trials.

Without such trials, we are losing valuable opportunities to determine whether these treatments are beneficial, harmful, or do nothing at all.

Mr. Chairman and Members of the committee, we need to get at the heart of these problems and barriers in order to overcome them.

I do not question that the officials testifying here this morning have a commitment, a deep one, to finding the means to treat and prevent AIDS. But more than two years of delays and foot dragging is too long.

I hope that today's hearing will enable us to find out and better understand what resources are needed, and what steps must be taken in order to ensure that access to drugs is increased and that clinical trials are expanded.

We do not need to, nor should we, compromise scientific integrity in the process. I believe that an appropriate balance between scientific vigor and compassion can be struck.

These are difficult and complex issues. And I again congratulate you, Mr. Chairman, and the committee staff and the committee Members, on your efforts to tackle them.

I look forward to hearing from the witnesses that will follow this morning, and I will continue working with you in developing sound and compassionate solutions.

Thank you very, very much.

The CHAIRMAN. Thank you very much, Senator Cranston.

Is it your impression that there was a good deal of hope a few years ago that there was going to be a faster track in terms of availability of experimental drugs, that were going to hopefully have some degree of efficacy and effectiveness, but was going to be able to be moved out into the community more rapidly, and that the community basically has been significantly disappointed, I would imagine is an understatement.

But is that what you're hearing from your constituency, from groups?

Senator CRANSTON. Yes, there was great hope and expectation. Those hopes and expectations have been dashed, and there is a great feeling that remedies that might be helpful just haven't been given an opportunity to be tested adequately and properly.

The CHAIRMAN. There's been the development of a whole underground, as I understand, in terms of various drugs and treatments as well that has grown up, as I understand, in California and other parts of the country.

Is this something that is for real?

Senator CRANSTON. Yes, it is very real. It is in California; it's in New York; it's elsewhere. And the problem is, people experiment without any real knowledge of whether it's going to be helpful or not.

And if it is helpful, or if it is harmful, or if it does nothing, there is no record of what has been accomplished, and therefore, little is learned from that.

The CHAIRMAN. This is primarily because of the frustration, is it?

Senator CRANSTON. Frustration and desperation.

The CHAIRMAN. Well, we would welcome you if you want to join us here. I know you have other programs. But I would ask our colleagues if they have any questions of Senator Cranston?

Senator MIKULSKI. I have no questions of Senator Cranston. The issues he raised were exactly raised by the PWAs that I met with a few days ago in Baltimore. And they do not want to be victims of quackery, but they don't want to be the victims of the sluggishness of their own government either.

Senator CRANSTON. That is a very unfortunate choice that they are faced with now. I thank you for the invitation. I will join you for awhile.

The CHAIRMAN. Thank you.

Our next witness, Admiral James Watkins, the Chairman of the President's AIDS Commission, former Chief of Naval Operations, who clearly brought his command talents to the commission.

In the opinion of many, Admiral Watkins literally saved the Commission from extinction. We welcome you here to this Committee, and we admire your commitment to public service, not only in the service of the flag of our country, but also, in so many good offices serving civilian needs as well.

We are delighted to have you here and look forward to your testimony.

STATEMENT OF JAMES D. WATKINS, CHAIRMAN, PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC, WASHINGTON, DC, ACCOMPANIED BY BURTON LEE, MEMBER, PRESIDENTIAL COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC; AND POLLY GAULT, EXECUTIVE DIRECTOR OF THE COMMISSION

Admiral WATKINS. Thank you, Mr. Chairman. I have also with me today Dr. Burton Lee, from Memorial Sloan-Kettering, New York, who is a member of the commission who I would like to have make comments before the committee also.

The CHAIRMAN. Welcome, Dr. Lee.

Admiral WATKINS. And also, my executive director, Miss Polly Gault.

The CHAIRMAN. Yes, we are very familiar with your staff here. Thank you very much. You have been a very effective person on this committee as a staffer. And we are all glad to welcome you back.

Admiral WATKINS. Thank you, Mr. Chairman, for this opportunity this morning.

I have provided to you and Members of the Committee a formal statement which I would like to have entered into the record.

The CHAIRMAN. It will be made a part of the record.

Admiral WATKINS. And in that formal statement, Mr. Chairman, I included a document which crosswalks many of the recommendations from our report with legislation which is being considered by this committee, in two different authorization acts.

Two of these bills are the Health Professions Reauthorization Act, in which we make certain recommendations in our report that I might think would be germane, and in addition, some possible amendments to the formerly passed bill, the NIH reauthorization

bill, passed by the Labor and Human Resources Committee in May, some of which I will talk about a little later, just perhaps for your interest and inclusion in your deliberation.

The CHAIRMAN. It will be included.

Admiral WATKINS. Also, I have included an update of a presentation that I gave before the House subcommittee on human resources and intergovernmental relations, which I think might be useful to the committee for the record.

[The statement referred to follows:]

TESTIMONY
BY

ADMIRAL JAMES D. WATKINS
U.S. NAVY (RETIRED)

CHAIRMAN
PRESIDENTIAL COMMISSION ON THE HUMAN
IMMUNODEFICIENCY VIRUS EPIDEMIC

BEFORE THE

HUMAN RESOURCES AND INTERGOVERNMENTAL
RELATIONS SUBCOMMITTEE

HOUSE OF REPRESENTATIVES

ROOM 2154, RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, D.C.

FRIDAY, APRIL 29, 1988
9:30 A.M.

UPDATED JULY 13, 1988

Mr. Chairman, Members of the Committee, I greatly appreciate the opportunity to testify today on the recommendations of the Presidential Commission on the Human Immunodeficiency Virus Epidemic regarding drug development to combat the AIDS virus. With me today is Dr. Frank Lilly, a Member of the Commission and Chairman of the Genetics Department at Albert Einstein College of Medicine. Frank is too modest to acknowledge his fine reputation as an expert in virology with a concentration on retroviruses so I will do it for him.

When the President asked me to assume the Chairmanship of the Commission in October 1987, we had not yet begun our substantive work to prepare a final report due in June 1988. After a few weeks on the job, and after meeting with and hearing testimony from a number of persons with AIDS, it became clear to me that drug development was one issue that deserved my immediate attention. As a result, we set the difficult goal of issuing an interim report on three subjects of immediate concern, one of which was drug and vaccine development. As you heard yesterday, for the person with AIDS, drug development is the number one issue--more important than education, prevention or debates about financing long-term care, and as you also heard, the lack of approved medications has driven persons with AIDS underground in search of unapproved drugs.

The Commission unanimously endorsed the recommendations you have before you which were presented to the President on March 15. I would like to highlight a few specifics in our recommendations, but first I would like to publicly answer for the record questions most commonly put to me.

1. Are the government and the private sector doing enough to develop new drugs and a vaccine?

No. The government, and I include the Congress here as well as the Administration, needs to do more to encourage much faster work in this area. Simply said, we were not ready to deal with a new infectious disease when it was first suspected in 1981. In fact, we as a nation, had become so chronically self-satisfied in our technological achievements in the health area that we had lulled ourselves into woeful unpreparedness to deal with a new virus when it suddenly appeared on the scene. Unfortunately, after seven years into this medical crusis, our bureaucracy is still struggling out of its lethargy. I do want to point out for the record that many senior federal officials have devoted countless hours at great personal scrifice to deal with AIDS. Three of them follow us today, Dr. Fauci, Dr. Hoth, and Dr. Young.

2. Why should we be spending all this money on AIDS research for one disease? Shouldn't we be spending more on the countless other diseases which have been afflicting Americans for hundreds of years?

We must spend these funds to find a cure for AIDS so that millions of Americans will not have to suffer and die from this awful disease. One way in which AIDS is different from other major diseases is that the death rates from cancer and heart disease, while unacceptably high, are not increasing markedly, while deaths from AIDS increase alarmingly each year. Therefore, the time to spend resources to slow this rate is now. From a practical point of view, we must find a medicine to intervene in the process of HIV infection to avoid slipping from an asymptomatic seropositive status to full blown AIDS. When we can do this, we will prevent untold suffering of millions of people, we will save enormous amounts of health care dollars, and we will have gained invaluable knowledge about the human immune system which will produce enormous benefits for all Americans and our internatinal neighbors afflicted with the myriad of other deadly diseases we all face. This work will help all Americans.

3. What are the best steps to take to improve the process?

In delving into just one of our chartered tasks, the Commission spent a lot of time deliberating how the process of drug development could be improved for this emergency. What we found was a jolt to me, an admitted novice to things medical.

First, the Food and Drug Administration (FDA), an agency charged with regulating the pharmaceutical industry, one of the most lucrative and productive industries in America, is operating out of a totally inadequate physical plant, with crippling manpower restrictions. While the National Institutes of Health (NIH) AIDS budget has increased from $3.4 million to $444 million in the past six years--that's a 10,000% increase--the FDA budget for reviewing the drugs produced by this accelerated research has stayed relatively flat. In fact, when the NIH budget is considered by the Congress in the Labor, HHS, Education Appropriations Subcommittee, the FDA budget is sent to another appropriations subcommittee--there is no linkage. Logic tells us that there should be some tie between incentives appropriated to enhance numbers of new drugs to to be developed, and hence ultimately reviewed, and the number of people provided to do the critically important review work.

FDA is the valve through which all AIDS drugs will eventually be regulated, whether they originate at NIH or

in the private sector. In the case of AZT, the FDA was able to review and license this drug in record time because the FDA has made AIDS a number one priority. But let's look at what they were forced to go through to accomplish this. They had to rob all their existing programs, pull people off of work on other life-saving drugs, to review and approve AZT. Why should people who need life-saving heart medications, or children who need specialized drugs for lethal childhood illnesses wait in line? Robbing Petor to pay Paul in generating defense hardware is one thing, but to play this game with deadly diseases is unethical from my point of view.

We know that our research efforts are beginning to pay off--many new AIDS drugs are already in the pipeline. But if we don't act now, no additional reviewers will be in place when those drugs reach the FDA. As a result, the backlog will be larger, and the delay in getting lifesaving drugs to persons with AIDS will be longer and more unconscionable than ever.

In addition to adding medical reviewers, we have also recommended a relatively inexpensive change in reviewing technique--one that could speed up review of clinical trials--and that is the development and use of computerized data sets. It is very hard to understand why the results of these trials must be submitted to the FDA on paper--approximately ten linear feet of stacked volumes--only to have the information taken off that paper and fed into computers for analysis. The FDA needs to enter the modern age of technology.

This country has the highest drug regulatory standards in the world. We are proud of that, and we should not accept any compromise in those standards to speed up drug review. But we also have the right to demand timely as well as accurate review, especially in the face of an escalating medical emergency. To reach this objective, we must provide the FDA with better technology and adequate numbers of skilled medical reviewers to do its job. We should discontinue the current practice of allowing the Office of Management and Budget to intimidate the FDA budgetarily without any apparent sensitivity to the adverse health consequences of their actions.

A second area of great concern in drug development is clinical trials. The "ACTG" system within NIAID has grown rapidly during the past year. In February, Dr. Fauci and Dr. Hoth testified before the Commission that National Institute of Allergy and Infectious Diseases (NIAID) had over 3,000 patients who were enrolled in or had completed trials of 17 drugs, in 35 medical centers across the country. Once again, we have the right to be proud of this success.

However, we are also anxious to open the doors to clinical trials to physicians and patients in community-based treatment settings for several reasons:

First, because treatment trials should be more widely available to those segments of the populations expected to represent the largest patient increase in the immediate future, namely women, children, intravenous drug users, and HIV-positive asymptomatic individuals. I.V. drug users are currently under-enrolled in trials, considering the large and increasing percentage of cases of AIDS they represent. This is a difficult patient group to treat, much less to included in rigorous trials, but they cannot be ignored, and the community-based centers may be our best hope. Health care workers testifying before the Commission provided compelling evidence that community care settings have greater contact with all of these patient populations than some medical research institutions;

Second, community-based trials will be helpful because we need to develop a larger cadre of physicians and other health care providers who are trained in the technical aspects of developing and administering clinical trial protocols; and,

Third, the community-based organization conducting clinical trials can be co-sponsored by pharmaceutical companies and, in some cases, private donations, thereby making the Federal contribution more cost effective.

Once again, we advocate no sacrifice of quality--all protocols would undergo the same rigorous approval process as one in any large medical center.

In addition, we would also advocate creating a training program for community-based physicians, which will provide them with access to the latest information about HIV and treatment for HIV-related illness, and will also help them develop expertise in the methods and specifics of admininistering clinical trial protocols. This program could be patterned after the successful Community Clinical Oncology Program initiated by the National Cancer Institute in the 1970's.

We are not alone in believing that the community-based trial setting could be an important research component. Representatives of the NIH and NIAID clinical trials program testified that they plan to develop such a program for all of the above reasons, and hoped to initiate funding within the next six months.

Another subject that has been raised frequently is

that of Treatment INDs. This program, begun with the best intentions of the FDA Commissioner, has not met the high level of expectation by the patient population that greater numbers of drugs would be made available to terminally ill people not enrolled in clinical trials. One year after the program's beginning, one drug has been approved for such use. The reasons for this failure to meet expectations are many and complex, and include such unresolved questions as:

-- What are the criteria for such early release?

-- What are the incentives for drug companies to participate in the program?

-- Who will pay for these drugs?

-- How would information on what is available under the program be disseminated?

-- How would manufacturers and physicians be protected from liability for toxic reactions to these unlicensed drugs?

If this program is to have any chance to succeed, these questions must be answered, and obstacles removed. However, the Treatment IND program will become a less volatile issue as more drugs are licensed, and accelerated drug development as a whole is our primary objective.

In summary, then, the most important things that can be done to improve the drug development process are:

-- Open drug trials to a broader spectrum of the infected population;

-- Eliminate wherever possible, even in private sector trials, the use of placebo controls, especially in patients with AIDS;

-- Continue to increase funding for basic and clinical research at the National Institute of Allergy and Infectious Diseases and the National Cancer Institute.

-- Increase the medical review work force, improve the facilities, and upgrade the technologic capacity of the FDA;

-- Centralize data collection for both research and public information purposes, to allow researchers to share information, and allow patients and physicians to know what trials

are available.

-- Remove the Treatment IND program obstacles.

To conclude, the Commission strongly supports these and other drug development recommendations in its Final Report, and looks to Congress for early action so that many of the obstacles in the way of developing palliative and curative therapies for HIV-related disease may be removed.

Admiral WATKINS. I'd like just to highlight some key recommendations, Mr. Chairman, that we made in our final report. This committee, more than almost any other committee in the Congress, is well aware of the details and the background, on these issues and I need not go into those.

I reported in the forwarding letter to the President that we had a unique opportunity to look at our society through what I called the lens of the HIV. We listened to 600 wonderful witnesses ranging from persons with AIDS, their families, and community-based organizations, all the way up to State and Federal officials.

And I will have to say that 90 percent of our report was their report. I clearly think this was the way to go. This process built consensus as we went along. We listened to the people out there. It was not 13 members sitting around a table divining this report. It was 600 great Americans, dedicated, courageous, many with AIDS, coming before us.

And we were able to listen to them and put together this particular report.

These are the highlights that I feel are important for this committee to hear this morning briefly.

First, comprehensive Federal antidiscrimination legislation needs to be enacted so that all persons with disabilities, including persons with HIV infection, will be protected when threatened with loss of job, housing, or services, solely on the basis of their HIV status.

Let me note that legislation, the Americans with Disabilities Act, S. 2345, is pending before the Subcommittee on the Handicapped of this committee which provides comprehensive antidiscrimination protection for people with disabilities.

I urge the committee to act on this legislation as soon as possible.

I cannot emphasize how important this particular piece of legislation might be to getting on with control of the epidemic. You will see it all throughout our report. You simply cannot get there from here, whether it is in health care delivery, whether it is in education, whether it is in therapeutic drug development, getting on with the kinds of things that Senator Cranston mentioned earlier, no matter where we turn, we find that antidiscrimination protection is critical to an efficient and an effective control of the epidemic.

The CHAIRMAN. Just before we leave that, to try and get it into some kind of perspective, as I understand, unless we are going to encourage the voluntary testing as enormously important in terms of the at-risk group, unless they're going to be assured of confidentiality and anti-discriminatory provisions you are not going to get the testing.

Admiral WATKINS. That's correct.

The CHAIRMAN. If you don't get the testing, you are not really going to get the handle on it. We can do the other parts which we need to do in terms of prevention education, which we ought to do.

But another key element, as I understand from your testimony and report, is that you have got to get the voluntary testing for the at-risk groups. There has to be confidentiality. You have to have sufficient provisions relating to people who may be at risk in terms of partners. And the ethical issues have to be worked out.

But then you have to have the anti-discriminatory provisions.

Admiral WATKINS. Absolutely, Mr. Chairman.

The CHAIRMAN. And I think this is enormously important, Admiral, because we have been able to move, and the country moves, on research; we do on education and training. But this is the other component which you have stressed.

And I just admire the fact that you have emphasized it, because I think it is absolutely key and absolutely essential.

I am a cosponsor of the Weicker-Harkin or Harkin-Weicker bill, but we have other ways, no matter what bill it is, those are the elements, as I understand.

Admiral WATKINS. Absolutely, those are the key elements, and it came from almost everyone of the witnesses. There was no question. From doctors, scientists, from persons with AIDS; you name it, hemophiliacs, wives of bisexual males who had no knowledge after 37 years of marriage that her husband was bisexual; the kind of story that Senator Mikulski reported, unfortunately are typical, not atypical.

The CHAIRMAN. Can I just get some idea, we are going to put you on the spot, what kind of reaction are you getting from the White House on this proposal?

Admiral WATKINS. As I have said publicly on many occasions, I am encouraged. I think it was a warm reception that I received. I think it was sincere.

The President reported out an anecdotal story of an individual that came to them personally, both he and his wife, and she described a story that touched every element that was in our report. And I think it made a big impact on the President.

I think when this epidemic touches any individual, all of a sudden you turn your other cheek and you really begin to understand the breadth and depth of this epidemic.

The CHAIRMAN. Well, I think just this provision on the anti-discriminatory, to the extent that we can get a warm response from the White House.

Admiral WATKINS. We will know in another 15 days.

The CHAIRMAN. We will give that assignment to you, Admiral.

Admiral WATKINS. In addition to that, Federal legislation providing protection of the confidentiality of HIV status, as you mentioned, needs to be enacted.

Specific exceptions to confidentiality, which are necessary to protect the public health, also need to be delineated.

And we for the first time, I think, have laid out in very discrete terms what those exceptions are. We may not have all of them, but we believe that they encompass the large body of those things that clearly make it in the best interest of individuals and the public health to breach confidentiality only in very specific circumstances.

The term AIDS, also, we believe is obsolete. We think it is time to move to HIV infection, because it more correctly defines the problem. HIV terminology should be used in order to focus our public policy and prevention effort on the full course of the HIV infection, rather than concentrating on the later stages of the disease.

As you know we are estimating 1 to 1½ million infected. That is the real issue. And obviously, we have to be very sensitive to those

with the clinical symptoms, and we have made many recommendations along those lines.

But I think too often the American people are misled by the term, 66,000, which is the latest report out of CDC, when we're really talking about 1½ million, and that may be underestimated. So I think this is very important that we begin to move now to those infected with the HIV. And that, of course, is coupled back to the antidiscrimination features, because we are asking that HIV and not just AIDS be included as a disability.

Prevention and treatment of intravenous drug abuse is another area of special interest, an important facilitator of the HIV epidemic, and it must become a top national priority.

Increased law enforcement effort to interrupt the supply of drugs must be coupled with greatly expanded treatment capacity with a goal of providing treatment on demand.

And I think that this is a very misunderstood area. Many think, well, why are we trying to spend all this money for drug abusers. That isn't the issue.

The issue is that we are trying to reach out and bring these people into contact with us so that we can touch them and begin to change their behavior, perhaps, and influence them.

And when they have a six month wait, three to six month wait for drug treatment, they simply are not going to come in in big numbers. We believe they will come in in big numbers if they can get treatment, and we will begin to send a signal to the country that we are serious about getting on top of drug abuse.

Age-appropriate comprehensive health education programs, placed in our Nation's schools——

The CHAIRMAN. Before we leave that, of course you know you are talking about big bucks.

Admiral WATKINS. Yes.

The CHAIRMAN. We do about 10 percent of treatment now, we do better in the areas of alcohol, and we still don't do enough on that, but we are still well behind in terms of the treatment, in terms of those who have addiction and who need treatment.

We are working out, as you know, trying to work, a bipartisan program in a number of the areas which you've outlined here. We have some difference between the two approaches and between the Republicans and the Democrats.

Our program is about $3 billion. That is about an additional 10 percent. We are dealing with 10, and we are going up an additional 10.

I mean, I think it is important for Americans to understand that if we are going to be serious about this, it is going to be costly. And particularly if you talk about treatment on demand, you are talking about enormous amounts of resources.

Again, this is going to be, where do we spend resources in our country. But we are talking a long period of time; wouldn't you agree with that?

Admiral WATKINS. A long period of time. We estimate just for intravenous drug abuse alone, there would be probably a ten-year program needed at $1.5 billion a year just for that, which represents only 20 percent of the drug addicts in the country, as you know.

But a very important vector, as you know, in the long term for the HIV spread.

The CHAIRMAN. You know what I would like to ask you to do. We are working out with our committees, now, we are meeting as a matter of fact later this week to try and work out the bipartisan program.

And there are very strong common provisions in both parts of the areas on the education and the treatment programs.

But I would like to ask you, you might do it in a bipartisan way, if you would be kind enough to just individually look over those particular provisions; not to take a position with regard to the commission, but for any of those, if you could take a look at those, and to give us at least the benefit of your counsel.

As I say, there is very substantial agreement in those areas, in the education, in the treatment. There may be some disparity in terms of the amounts of resources, but if we can get a common position it would be very helpful.

So we will ask on behalf of the committee to work out, if we could do it without any formal kind of request, we will ask your review of those.

Admiral WATKINS. We have worked extensively with your staff people, Mr. Chairman. And in fact, many of our recommendations are in your current AIDS bill. Additionally, many of our drug abuse suggestions are in both the Republican and Democratic drug proposals.

The CHAIRMAN. Absolutely.

Admiral WATKINS. So we will continue to work with you on that.

Age-appropriate comprehensive health education programs placed in our Nation's schools by the year 2000, kindergarten through grade 12, should be a national priority. I was appalled to hear from the best health educators, public health officials in the Nation, that they give the Nation's health education, health promotion programs in our school a grade of D-minus for this Nation.

We simply do not know anything about our own human biology, and we are not allowing our young people to be part of the solution to their own problems. They are bright kids. They can understand themselves, and begin to learn a little bit about their own human dignity and perhaps respect others in the process.

So we think this is a very important additional program that we cannot assume is long range. It is here now. Large numbers of kids going into our kindergartens and first grades now, and we must get serious about health education and health promotion, not extracurricular, but curricular.

So we have made some strong recommendations in that regard, and I think it is time to move the Nation. So I would hope in your other hats, that this would be an important part.

The CHAIRMAN. Early education is important?

Admiral WATKINS. Absolutely. It is absolutely critical. And in health, of course, you go all the way back to prenatal; let alone preschool head start. And all the best pros in the field, including the committee on economic development, 250 entities of business leaders, are all proposing this, particularly as it affects disadvantaged.

So this is an extremely important part of our findings. And I highlight it here this morning because I think sometimes we think

of HIV specific education as the answer to the epidemic, when in fact we are not building a set of blocks for our young people to begin to understand what they are all about.

The expected 10,000 to 20,000 HIV-infected births by 1991 indicates a critical need for the development of support services for intact families and recruitment of foster families for these infants.

Available services such as day care, home care, respite care, psychosocial services, would decrease the number of hospitalizations of children with AIDS, possibly improve their quality of life, and help maintain the intactness of the natural family.

I cannot tell you how important this is. Senator Mikulski mentioned one example. We have seen hundreds of them out there. We went to the Harlem Hospital, the Metropolitan Hospital. We went to Jackson Memorial in Miami. These are very, very important issues.

And people don't link discrimination to infants with AIDS, but it is there. They can't get the foster homes. They can't even move into private residences because of the threat of burning out of a home or whatever.

It is one of the situations in the AIDS epidemic that I don't think the American people understand. Ten to 20,000 infants with AIDS by the year 1991. A thousand alone will be born in New York this year.

So this is going to finally tear at the heartstrings of even the extreme individuals who attack AIDS patients. And finally it may get the national awareness up to the point where we really declare war on AIDS.

Special attention needs to be given to equitable and cost-effective means of financing care for persons with HIV infection. I believe we have the potential for a more cost-effective health care delivery system, and the possible amortization for the up front investments.

I think too often we look at up front investments, such as the dollars on drug treatment, and say, that is just going to be an up front investment. I don't think our cost analysts do a very good job when we get into human resources, and I think there are areas where we can show prospective amortization over a short period of time, and get into prevention much more aggressively than the continued national policy, de facto national policy, of remediation.

And I think it is time again to move into a much more cost effective health care delivery system. And we have made some recommendations along those lines.

Clinical trials for HIV drug treatment should be expanded to utilize community based research organizations, particularly with participation of women, children, hemophiliacs, intraveneous drug abusers.

This is along the lines that Senator Cranston mentioned earlier. We think it is very important to have——

The CHAIRMAN. Primary care doctors?

Admiral WATKINS. Primary care. Because we believe that when you have the set of unknowns as we do surrounding this epidemic, no cure, no vaccine, a lot of confusion at the outset of this epidemic, that we need to have a balance between those research entities working clinical trials, for example, that deal with more scientific data, and those community doctors who deal more with treatment.

And yes, by the way, we can give you some scientific support as well. So we think that is a very important adjunct at this phase in the epidemic.

Finally, drug development and approval procedures, as well as increased incentives for drug development and expedited availability, need improvement. And we have pointed out, in my formal statement, under the section that is recommended for your inclusion as possible amendments to a previous passed bill, that you look at recommendation 4–14.

We really believe that NIH needs to be freed. They're imprisoned by OMB right now in a number of areas. And I believe that it is very important that Dr. Wyngaarden and Dr. Broder and Dr. Fauci be given a top line yes, and a top manpower ceiling; okay. But then let them alone.

Let us get out of the micromanagement that is going on right now in this particular area. I think it is very, very detrimental to the efficient operation of NIH.

And I think it is so important that I have made a strong recommendation, even in my presentation to the President. I think this is one area we can move right away on.

Give them a break. Give them a chance to manage. There is a whole ring out there for clinical trials on AIDS that they can't operate; it is sitting there idly because they cannot migrate the manpower ceilings, the FTEs, properly within their own budget top ceilings.

Now this is ridiculous. Bureaucrats with control over NIH are three levels down. And here we have the best research facility in the world held up by functionaries at some low level that can't simply move some resources within their total allocation.

So we are making some strong recommendations; a strong letter follows if you will.

Senator MIKULSKI. Bravo, bravo. Fire at will, Admiral.

Admiral WATKINS. With that, Senator Kennedy, I will pass it on to Dr. Lee, who will follow up on some NIH-specific information that I know the committee is interested in.

[The prepared statement of Admiral Watkins follows:]

TESTIMONY BY

ADMIRAL JAMES D. WATKINS
UNITED STATES NAVY (RETIRED)

CHAIRMAN
PRESIDENTIAL COMMISSION ON THE HUMAN
IMMUNODEFICIENCY VIRUS EPIDEMIC

BEFORE THE
U.S. SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
JULY 13, 1988
WASHINGTON, D.C.

GOOD MORNING, MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE. THANK YOU FOR THIS OPPORTUNITY TO TESTIFY BEFORE THE LABOR AND HUMAN RESOURCES COMMITTEE. WITH ME TODAY IS DR. BURTON LEE, A FELLOW COMMISSIONER AND SENIOR PHYSICIAN OF THE LYMPHOMA SERVICE AT MEMORIAL SLOAN-KETTERING CANCER CENTER IN NEW YORK. DR. LEE'S EXPERIENCE AS AN ATTENDING PHYSICIAN FOR AIDS PATIENTS AT SLOAN-KETTERING HAS MADE HIM ESPECIALLY VALUABLE ON OUR COMMISSION.

BEFORE PROCEEDING I WOULD LIKE TO ACKNOWLEDGE THE FINE WORK THAT THIS COMMITTEE HAS DONE IN EXAMINING THE HIV EPIDEMIC, AND IN PARTICULAR IN SECURING THE FULL SENATE'S ENDORSEMENT OF S. 1220, THE AIDS RESEARCH BILL. THE COMMISSION WAS ESPECIALLY PLEASED TO SEE SEVERAL OF OUR RECOMMENDATIONS INCLUDED IN THE LEGISLATION. THE LEADERSHIP OF SEN. KENNEDY, SEN. HATCH AND OTHER COMMITTEE MEMBERS IN THIS AREA IS NOTEWORTHY.

I WOULD LIKE TO USE THIS TIME TO HIGHLIGHT RECOMMENDATIONS OF THE FINAL REPORT OF THE PRESIDENTIAL COMMISSION ON THE HIV EPIDEMIC. AS YOU KNOW, I DELIVERED THE REPORT TO THE PRESIDENT ON JUNE 24, ON BEHALF OF ALL THE COMMISSIONERS.

OUR COMMISSION SPENT OVER 9 MONTHS LISTENING TO TESTIMONY FROM OVER 600 OF THE MOST KNOWLEDGEABLE WITNESSES ON THE HIV EPIDEMIC THAT COULD BE ASSEMBLED. WE WERE TASKED BY THE PRESIDENT TO EXAMINE THE PUBLIC HEALTH, MEDICAL, LEGAL, ETHICAL, SOCIAL AND ECONOMIC IMPACT OF THE HIV EPIDEMIC AND MAKE RECOMMENDATIONS TO

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IMPROVE OUR NATION'S RESPONSE TO THE EPIDEMIC. OUR FINAL REPORT INCLUDES ALMOST 600 RECOMMENDATIONS, SEVERAL OF WHICH FALL UNDER THE PURVIEW OF THIS COMMITTEE'S JURISDICTION.

IN ESTABLISHING THE COMMISSION, THE PRESIDENT AFFORDED AN UNUSUAL OPPORTUNITY TO VIEW CONTEMPORARY AMERICAN SOCIETY THROUGH THE LENS OF THE HIV. FLAWS OF OUR NATION'S HEALTH CARE SYSTEM AND WEAKNESSES IN THE FABRIC OF OUR SOCIETY WERE EXPOSED TO US IN VIVID DETAIL. WE SAW FIRSTHAND:

- AN OVER-BURDENED AND OVERLY EXPENSIVE HEALTH CARE DELIVERY SYSTEM.

- A TERMINALLY SLOW THERAPEUTIC DRUG DEVELOPMENT PROCESS WHICH IS NO MATCH FOR THE NEARLY DAILY SCIENTIFIC SURPRISES WHICH SEEM TO SURROUND THIS VIRUS.

- AN INEFFECTIVE ADDRESSAL OF DRUG ABUSE AS A SIGNIFICANT NATIONAL THREAT BY ALL LEVELS OF SOCIETY.

- THE ABSENCE OF AN INTEGRATED HEALTH EDUCATION AND HEALTH PROMOTION CURRICULUM IN OUR SCHOOLS AND WORK PLACES, PROVIDING US NO READY REPOSITORY FOR DEALING IN A FUNDAMENTAL WAY WITH OUR OWN HEALTH -- WHETHER IN NUTRITION, SUBSTANCE ABUSE, TEEN PREGNANCY, OR WHATEVER. SADLY, WE STILL SEEM TO HAVE A PENCHANT FOR

THE REMEDIAL, THE PIECEMEAL, THE "BAND-AID" APPROACH FOR EVERY NEW HEALTH CRISIS ... THE "KNEE JERK" RESPONSE IF YOU WILL.

- A HEALTH CARE PROFESSIONAL EDUCATION PROCESS ALSO UNRESPONSIVE TO A NEW, FAST MOVING, AND DECEPTIVE MEDICAL THREAT LIKE THE HIV. FOR EXAMPLE, DOCTORS, NURSES, DENTISTS, PARAMEDICS, POLICEMEN, FIREMEN, VOLUNTEERS, SOCIAL WORKERS AND ALL WHO COME INTO DIRECT CONTACT WITH HIV INFECTED INDIVIDUALS SHOULD BE AMONG THE FIRST RECIPIENTS OF THE BEST, SCIENTIFICALLY-BASED, EDUCATION MATERIAL AVAILABLE ON THE HIV. BUT ARE THEY? ... ALAS, NO. NOT EVEN TODAY -- SEVEN YEARS AFTER THE EPIDEMIC WAS FIRST RECOGNIZED.

- A SOCIETY STILL TOO QUICK TO REJECT, DENY, CONDEMN AND DISCRIMINATE, ALBEIT NOT UNLIKE PAST CLASSIC RESPONSES TO NEW INFECTIOUS DISEASES WHEREIN IGNORANCE OF SURROUNDING SCIENTIFIC FACTS ABOUNDS FOR TOO LONG AT THE DISEASE'S OUTSET. THIS, OF COURSE, LEADS US DOWN THE PATH OF TOO MANY FALSE STARTS IN DECISION MAKING.

- A HEALTH CARE DELIVERY SYSTEM INCREASINGLY WEAKENED IN QUALITY BY SHORTAGES OF THOSE WHO MAKE THE SYSTEM WORK, LIKE NURSES, AS WELL AS MANY OTHERS IN A VARIETY OF CRITICAL SPECIALTIES OF MEDICAL PRACTICE ... SHORTAGES

PREDICTED FOR YEARS BY THE PROS, YET LITTLE DONE HERETOFORE TO ADDRESS THIS PROBLEM EFFECTIVELY.

- AN INCREASINGLY LITIGIOUS AND ADVERSARIAL RELATIONSHIP BETWEEN PROVIDERS OF HEALTH CARE AND CONSUMER, BE IT THE DOCTOR-PATIENT RELATIONSHIP, THE VACCINE DEVELOPER-VACCINE RECIPIENT, OR HOSPITAL-PATIENT. THE UNINTENDED RESULT OF THIS FRICTION IS WITHDRAWAL BY HEALTH CARE PROFESSIONALS OF NEEDED SERVICES. THIS CAN RANGE FROM REFUSAL TO CARE TO A REFUSAL TO TAKE RISKS IN VACCINE AND DRUG DEVELOPMENT -- IN ANY CASE LEAVING THE PATIENT WITH FEW OPTIONS.

WHILE THE WORLD OF THE HIV EPIDEMIC WHICH WE VIEWED WAS SOMBER AND GRIM, WE ALSO WITNESSED THE OTHER SIDE OF THE EQUATION. WE WITNESSED THE INCREDIBLE GOODNESS AND FUNDAMENTAL COMPASSION OF THE AMERICAN PEOPLE ACROSS THE NATION. WE WITNESSED AN AMERICA READY TO REAFFIRM THE BASIC VALUES OF COMPASSION, JUSTICE AND DIGNITY, FROM HEALTH CARE WORKERS TO VOLUNTEERS IN COMMUNITY-BASED ORGANIZATIONS TO LOCAL FIREMEN, POLICE AND EMERGENCY WORKERS. WE WITNESSED YOUNG PEOPLE WHO DEMONSTRATE PERSONAL BRAVERY AND DECENCY IN STANDING UP FOR THEIR HIV-INFECTED CLASSMATES WHO HAVE BEEN SUBMITTED TO THE VILEST OF ATTACKS BY BULLIES INSIDE AND OUTSIDE THEIR SCHOOLS. WE HAVE HEARD FROM BUSINESS LEADERS, CHURCH AND OTHER HUMANITARIAN GROUPS WHO HAVE REFUSED TO SUCCUMB TO THE OVERLOAD OF WORK PLACED ON THEM OR THE

SAME OLD TIRED BUREAUCRATIC OBSTACLES THROWN IN THEIR WAY AT EVERY TURN AS THEY MOVE TO MEET DAILY LIVING NEEDS OF HIV-INFECTED PERSONS.

THE HIV EPIDEMIC, THEN, HAS BEEN MUCH MORE THAN A MEDICAL CRISIS OR A PUBLIC HEALTH THREAT. WHILE WE FOUND IT TO BE A GRAVE TRAGEDY, WE ALSO FOUND IT TO BE AN OPPORTUNITY TO CONFRONT AND BEGIN TO SOLVE MANY OF THE PROBLEMS OUR SOCIETY FACES.

LET ME HIGHLIGHT SOME OF THE KEY RECOMMENDATIONS WE MADE IN OUR FINAL REPORT IN THE AREAS OF PREVENTION, CARE AND CURE:

- PREVENTION AND TREATMENT OF INTRAVENOUS DRUG ABUSE, AN IMPORTANT FACILITATOR OF THE HIV EPIDEMIC, MUST BECOME A TOP NATIONAL PRIORITY. INCREASED LAW ENFORCEMENT EFFORTS TO INTERRUPT THE SUPPLY OF DRUGS MUST BE COUPLED WITH GREATLY EXPANDED TREATMENT CAPACITY WITH THE GOAL OF PROVIDING TREATMENT ON DEMAND. WHILE UP FRONT INVESTMENTS IN PREVENTING AND TREATING DRUG ABUSE ARE SIGNIFICANT, THEY ARE COST-EFFECTIVE IN THE LONG RUN, FOR TREATMENT FOR DRUG ABUSERS IS A CRITICAL PREVENTION TOOL FOR THE SPREAD OF THE HIV.

- AGE APPROPRIATE, COMPREHENSIVE HEALTH EDUCATION PROGRAMS PLACED IN OUR NATION'S SCHOOLS BY THE YEAR

2000, IN KINDERGARTEN THROUGH GRADE TWELVE, SHOULD BE A NATIONAL PRIORITY.

- THE CONCERNS OF HEALTH CARE WORKERS NEED TO BE BETTER ADDRESSED SO THAT COMPLETE INFORMATION ABOUT HIV IS PROVIDED AS WELL AS ADEQUATE PROTECTIVE MATERIALS AND A SAFE WORKING ENVIRONMENT IN WHICH TO PROVIDE COMPREHENSIVE AND COMPASSIONATE CARE.

- COMPREHENSIVE FEDERAL ANTI-DISCRIMINATION LEGISLATION NEEDS TO BE ENACTED SO THAT ALL PERSONS WITH DISABILITIES, INCLUDING PERSONS WITH HIV INFECTION, WILL BE PROTECTED WHEN THREATENED WITH LOSS OF JOB, HOUSING OR SERVICES SOLELY ON THE BASIS OF THEIR HIV STATUS. LET ME NOTE THAT LEGISLATION, THE AMERICANS WITH DISABILITIES ACT, S. 2345, IS PENDING BEFORE THE SUBCOMMITTEE ON THE HANDICAPPED OF THIS COMMITTEE WHICH PROVIDES THE NEEDED COMPREHENSIVE ANTI-DISCRIMINATION PROTECTION FOR PEOPLE WITH DISABILITIES. I URGE THE COMMITTEE TO ACT ON THIS LEGISLATION AS SOON AS POSSIBLE.

- SPECIAL ATTENTION NEEDS TO BE GIVEN TO EQUITABLE AND COST-EFFECTIVE MEANS OF FINANCING CARE FOR PERSONS WITH HIV INFECTION. A SERIES OF DEMONSTRATION PROJECTS INVOLVING THE PUBLIC AND PRIVATE SECTORS NEED TO BE

UNDERTAKEN, AS THE FINANCING OF CARE WILL PRESENT MORE AND MORE OF A CHALLENGE AS THE NUMBER OF SYMPTOMATIC INFECTED PERSONS INCREASES.

- FINALLY, BIOMEDICAL RESEARCH AND DRUG AND VACCINE DEVELOPMENT EFFORTS NEED TO BE ENHANCED. INCREASED FLEXIBILITY AT THE NATIONAL INSTITUTES OF HEALTH AS WELL AS STREAMLINED DRUG DEVELOPMENT APPROVAL PROCEDURES AND INCREASED INCENTIVES FOR DRUG DEVELOPMENT AND EXPEDITED AVAILABILITY ARE CRITICAL.

MR. CHAIRMAN, THAT CONCLUDES MY FORMAL TESTIMONY. I HAVE HERE AN UPDATED VERSION OF THE TESTIMONY I PRESENTED TO THE HOUSE SUBCOMMITTEE ON HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS REGARDING BIOMEDICAL RESEARCH AND DRUG DEVELOPMENT, WHICH I WILL SUBMIT FOR THE RECORD. I WOULD ALSO LIKE TO SUBMIT A DOCUMENT WHICH CROSSWALKS RECOMMENDATIONS FROM OUR REPORT WITH LEGISLATION WHICH IS BEING CONSIDERED IN THIS COMMITTEE, SUCH AS THE HEALTH PROFESSIONS REAUTHORIZATION ACT WHICH I BELIEVE YOU ARE MARKING UP TOMORROW.

THANK YOU FOR THIS OPPORTUNITY AND I WILL BE HAPPY TO RESPOND TO THE COMMITTEE'S QUESTIONS.

The CHAIRMAN. You can tell that you are going to get some response in just a moment on this. But Senator Stafford is necessarily going to have to absent himself, and I would like to yield to him first, and then we will move on.

Senator STAFFORD. Thank you very much, Mr. Chairman. I have a brief opening statement. I would ask unanimous consent that it appear in the record as if read.

And I would congratulate the Admiral on his statement here, on his written statement, which will be in the record, and on the work of the Commission.

I thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much.

Burt Lee, we are very glad to have you here. You have had a very distinguished record at Memorial Sloan-Kettering, and I know you have been very active in the community physicians programs in getting this out.

We would like to hear from you.

Dr. LEE. Thank you, Senator Kennedy.

I want to congratulate Senator Stafford, too, for having been able to control Polly Gault for many years. I want to say hello to my old friend, Senator Weicker, and greet Senator Mikulski and Senator Cranston.

Senator STAFFORD. Dr. Lee, I think you overestimate my control.

Dr. LEE. I want to echo, as a Commissioner, my own feelings about Admiral Watkins. He deserves all the commendations that he gets; he deserves all of it, as does Polly Gault, and as do all of our staff members.

A lot of them are here today, and I want to read their names, because without them, this report would not be published.

And Jane West, Sherry Kaiman, Nancy Wolicki, Jackie Knox, and Peggy Dufour at the end of the table deserve one hell of a lot of credit.

Governor DiPrete from Rhode Island, in his testimony before us, gave us a statement which stuck with me. He said the first business of government is to protect its citizens.

AIDS is going to kill 250,000 people in the next four years. I am here not to talk about anything but one recommendation that we have made: education and prevention are a holding action. They are terribly important; that's all we have now. But the name of the game is research.

This was stressed by Lew Thomas at our first meeting at Memorial back last September. And it is what we end up with today.

We went out to NIH with a couple of the business people on our commission who listened carefully to what is happening out there, to the Director of NIH, who didn't complain, but many of the people who worked there told us about how the budget proposals, the personnel proposals, have to carry up through the Public Health Service, HHS, OMB, and come back. And basically the Director has lost control of his organization.

We are recommending, and this committee is the committee that has the authority to do it, that the NIH be cut loose, that the Director report directly to the Secretary of Health; that their budget come down from OMB; and that it not be micromanaged by OMB;

that the director of NIH handle his own money, handle his own personnel; restructure priorities as he sees fit.

Free him up. Give him some room to run. The name of the game in research is innovation. And you cannot do it the way this institution is structured at the present time.

Now what are the other spinoffs of allowing NIH to cut loose? AIDS research is virus research. When we talk about drug trials, you have to realize that the medical profession does not have any truly effective drugs for viruses.

In medical history, we do not have the tools at the present time. An enormous amount of research has to be done before these are going to be developed.

As these viruses are being worked on, we are going to find out the causes of cancer, and we are going to find out the causes of many of the degenerative diseases that affect old age.

Now, Admiral Watkins adopted the format in our report of obstacles to progress. Constraints on the NIH represent the major obstacle to progress which we have identified.

Please, members of this committee, help us to remove this obstacle and allow a truly great institution to thrive again.

Thank you.

[The prepared statement of Dr. Lee follows:]

TESTIMONY BY

BURTON J. LEE, M.D.
COMMISSIONER

PRESIDENTIAL COMMISSION ON THE HUMAN
IMMUNODEFICIENCY VIRUS EPIDEMIC

BEFORE THE
U.S. SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
JULY 13, 1988
WASHINGTON, D.C.

Good morning, Mr. Chairman, and members of the Committee. Admiral Watkins has already discussed some of the many large issues uncovered by our Commission relative to this nation's health care system, and our drug and vaccine development programs.

This morning, I would like to focus on the one recommendation in our report that I believe could make the single largest difference to the American people, and people the world over, with respect to research, drug and vaccine development. That recommendation is on page of our report, and deals with the National Institutes of Health.

We say in our report that "the mandate of science is exploration and discovery, and this requires flexible management to allow for the creative application of ideas." For far too long, this nation's most prominent research university, the NIH, has been constrained by oversight and management practices that have not allowed this to happen. Micromanagement by OMB, the slow response of other government agencies to NIH requests, and the lethargy inherent in any bureaucracy as large as HHS all conspire to slow the tremendous progress for which NIH is known, and of which it is capable.

For these reasons, our Commission endorsed what we refer to as the "NIH amendment" during our final deliberations. The text of this amendment is before you. We strongly believe that the NIH should not be micromanaged by OMB.

When we analyze the research problems related to HIV, the obstacles to progress, and possible ways to facilitate progress, we focussed on the NIH as one of the principal tools we have as an nation to fight this war. After all, the NIH is where the HIV was discovered.

The NIH sits deep within the Public Health Service, which itself is a subsection of HHS. When the Director of the NIH wants to make changes of any kind, or focus on a new problem of particular importance, he must make his requests for personnel slots and financing through three separate levels of bureaucracy through the OMB. The result is that the Director of the NIH, and the Directors of the subsections of the NIH, end up with little control over the staffing, management, operations, and salaries within their departments.

We conclude that this is no way to run a university. No research arm of any institution can prosper under such bureaucratic control and red tape. The ability to innovate, which is the essence of science and discovery, become strangled. We have concluded that the NIH should be cut loose from these constraints, and we have suggested legislation to effect this.

The Director of the NIH should report directly to the Secretary of HHS. OMB should be suspended from micromanaging its budget. Give the Director a budget directly through the Secretary of HHS, and let the Director manage and distribute his own money the way he sees fit. Let him be held accountable. These people want to be held accountable. But give them the freedom to act, to recruit, to create, to innovate. Please do not let one of the truly great educational and research institutions in the world gradually collapse by strangling its ability to change and react, which is what is happening today.

Lastly, look at the spin-offs. AIDS research is virus research. Virus research is a frontier in medicine that has been scratched, but remains today almost untouched. As we find out more about these viruses we will rapidly get to the heart of many other problems, such as cancer, and many of the degenerative diseases associated with aging. We will find out many of the truly basic facts about our own living cells, and about life. An active, growing, vibrant NIH stimulates similar research throughout this country, and world-wide.

I have seen how difficult to change anything in this government of ours. I do not have to tell you that the momentum of government institutions and programs is awesome. But you are the people who can do this. You are the only people who can do this. We have submitted a summary of some of our recommendations regarding the NIH. I hope that you can include some of these ideas in your proposed legislation, particularly see Chapter 4, recommendation number 14, page 44.

Governor DiPrete of Rhode Island, in his testimony to us, told us that the first business of government is to protect its citizens. We agree. In the HIV epidemic, prevention and education techniques are a holding action. If victory is to be gained, it must be gained through research.

Thank you.

The CHAIRMAN. Thank you very much.

I will just take a couple of minutes as I've inquired. When you talk, Admiral Watkins and Dr. Lee, about the management by OMB, and the stifling of various research, we have over here the administrative confidential request that was actually made in Fiscal Year 1988 in the effort on the AIDS research program.

The request, as I understand, is $750 million, of which the OMB had actually approved $285 million, and eventually it was moved up to $422, and the Congress ended up giving $470.

So we are talking about just about barely half of what was actually indicated by those who represent the tops in terms of research, how resources could actually be effectively managed, those as a result of scientific review. And thought that in those particular items—I am not going to take the time of the committee; we will submit the chart in its entirety in terms of the hearing

[The chart referred to follows:]

FCRDSEN
DHV/DPE/EI
5 Dec 88

ADMINISTRATIVE CONFIDENTIAL

AIDS 1990 EXERCISE: SUMMARY BY FUNCTIONAL CATEGORY
(Dollars in thousands)

	1986	1987			1988			1989	1990
	Actual	Approp.	Add'l.	Total	Request to CPB	Add'l.	Total		
1. Pathogenesis & clinical manifestations:									
*a. Epidemiological studies	927,848	536,172	86,340	942,512	849,237	844,057	993,295	911,457	817,384
b. Virology lab	2,983	3,321	926	4,247	4,034	4,527	8,561	12,063	12,280
c. Surveillance	2,262	2,738	1,076	3,814	2,743	6,384	9,127	6,654	6,341
*d. Etiologic agent and co-factors	13,069	23,532	2,791	26,323	28,275	24,436	52,711	62,126	77,822
*e. Immunologic studies	14,295	15,849	3,320	19,169	17,302	11,630	28,932	30,536	36,632
f. Vision AIDS	3,541	4,412	312	4,724	5,926	572	6,498	5,617	6,281
g. Psychosocial factors	39	62	0	62	64	1,805	1,869	1,896	1,963
h. (Unassigned)	n/a	n/a	1,252	1,252	n/a	6,875	6,875	9,366	10,379
Subtotal	64,017	86,086	16,017	102,103	107,581	100,286	207,867	239,715	286,306
2. Therapeutics:									
*a. Studies of therapeutic intervention	38,637	87,223	5,976	93,197	92,491	91,628	184,119	208,356	262,885
b. Drug purchase & distribution	9,364	14,676	0	14,676	28,625	7,391	36,016	34,272	36,250
Subtotal	48,001	101,899	5,976	107,873	121,116	99,019	220,135	319,226	299,135
*3. Vaccine development & evaluation	13,300	26,887	0	26,887	42,266	16,326	58,588	87,819	101,340
4. Public health control measures:									
a. Information dissemination/public affairs	1,602	1,302	0	1,302	1,675	2,000	3,675	3,535	3,696
b. Health education/risk reduction	0	0	1,392	1,392	0	4,655	4,655	5,660	5,265
c. Prevention of transfusion-related AIDS	622	1,132	0	1,132	1,765	10,135	11,900	10,740	11,565
d. Development & evaluation of blood tests	6,866	7,797	50	7,847	8,929	4,233	13,162	6,220	6,600
Subtotal	9,170	10,431	1,442	11,873	11,869	21,023	32,892	25,955	27,686
5. Patient care & health care needs:									
a. Treatment demonstration projects	95	100	0	100	101	1,540	1,642	10,500	11,000
b. Bioethics & biosafety	84	90	0	90	90	0	90	97	99
Subtotal	179	190	0	190	192	1,540	1,732	10,597	11,099
6. Multidisciplinary AIDS research	n/a	22,450	6,696	29,146	2,828	102,036	104,864	210,856	299,303
7. Facilities, equipment, & construction	n/a	n/a	180	180	n/a	126,380	126,380	46,400	48,867
TOTAL	134,667	247,943	30,309	278,252	285,850	466,608	750,458	940,568	1,153,625

The CHAIRMAN. But I think the way you can read this particular chart, and the fair way to read it, is that there was a lot that could be done, a lot of important work that could be done, that was based upon sound, scientific research and clinical research and other research that they thought was justified.

It was recommended to go from the 750 down to 285, by OMB. And we won't take the time of this Committee to go through how many researchers they have, or how many scientists, or how many doctors. But it wouldn't be on one hand.

And they have effectively made the decisions. And then there were some appeals. And the Congress added some additional funds.

But it is still dramatically inadequate. We will get into other aspects of this whole challenge, whether resources, administration, approval of drugs, other factors. But the point I hear you saying very clearly is, do not emasculate the whole effort that can be made when you have important and significant scientific possibilities by having sort of the gray hand of OMB making the judgment decision about national priorities and resources in this.

Money isn't going to solve all the problems, but it is a pretty clear indication of what our priorities are as a society. And I imagine this type of thing is what you are talking about?

Admiral WATKINS. Exactly. You here in the Congress have provided the additional resources. And I don't want to speak for Dr. Weingarten or Tony Fauci who will be coming before this committee shortly.

But I believe that their complaint to us clearly was not the top-line dollar that Congress allowed. It was their inability to manage that dollar efficiently and effectively from within the institution.

That is what we are driving at. So they are not asking for more than the Congress is providing. You, Senator Weicker, and others have been outspoken, and have really put the dollars in at about the right level.

So the NIH is not complaining about that. What their complaint is, really, at the top level management, is they cannot manage those dollars efficiently inside the system without a very constipated process that they have to go through that makes it very difficult for them to efficiently carry out their mission.

This is a fast-moving set of unknowns that they have to deal with. And they do not have a fast-moving system, a dynamic system, that allows them to do it.

So it is inside the total, and you are absolutely right. What has happened is, OMB, which by the way was not very receptive to our commission when we went over to find out what was going on.

So it seems to me they sit there making judgments as a surrogate secretary for medical research in the Nation without portfolio.

The CHAIRMAN. This document was at the request of the White House, the Office of Science and Technology in 1986, it was said, what would be necessary if you pulled out all the stops and presented a realistic budget, and there were no budget limitations.

And that is what this particular program represented to be the best.

Senator WEICKER. Would the Senator yield?

Two points that should be made. As you know, I chaired, and still sit as ranking member on the Labor-HHS-Education appropriations subcommittee.

And the question has been asked, each of the last four years, as to who OMB has on their staff passing upon this budget that has medical qualifications or scientific qualifications. It is not a question of five. You put up your hand, indicating less than the fingers on your hand. But the answer really is none, zero. Absolutely zero.

Point number two, the Senate, for the last three years, has insisted on FTE totals being met. The House has not accepted on that provision, although I gather they will this year.

So whether it is the employees, whether it is the management of the money, whether it is the expertise the passing of the budget should be. And believe me, not only have you been given a hard time as a commission, but so has the entire Congress of the United States, and therefore, the people of the United States, by a group that has absolutely no qualification at all, either to set the totals or to manage.

Admiral WATKINS. Senator Weicker, I couldn't agree more. And I think what has happened here is that this has given rise to an imbalance in the system.

And I pointed out one example of this, which is the separation of the FDA budget vis-a-vis the NIH budget. In other words, all of this system is a total system that should be coupled together. And if there are going to be budget cuts that the Congress feels are necessary and the White House feels are necessary, fine, but they should be balanced.

But for God's sake, let's make them in some kind of balanced form so that we end up with programs that aren't totally out of synchronization.

If everything pouring into NIH is going to come to fruition, and we leave a flat loaded budget in FDA, I don't see how we're going to manage the efficacy, the trials, and all of the things that FDA has to do.

So it is not just for NIH alone. It is the system that is out of balance because of these arbitrary decisions made in my opinion by OMB to put screws on these various line items.

And they do not have the expertise to be able to balance it back into the system, much as we have to do in every other appropriation.

The CHAIRMAN. There are about four or five minutes left on this vote, and then we will reconvene. So we will have a short recess.

[Brief recess.]

The CHAIRMAN. We want to move on with our hearing. But I did have a final question for Admiral Watkins.

In reading the final report of your Commission, I get the clear impression that since the AIDS crisis began, the Administration has not provided the extra manpower to the National Institutes of Health to meet the emergency.

In fact, NIH has actually lost more than 1,000 employees in the face of this health disaster.

First of all, is it your understanding that we have lost 1,000 employees?

Admiral WATKINS. Dr. Lee can answer that.

Dr. LEE. Senator Kennedy, on page 42 of our report we summarize some of this. A total of 371 new FTEs were put in for HIV. But they lost overall 1,032 FTEs at the center.

Now this is OMB telling Weingarten and Vince DeVita, for instance, that he is going to lose so many positions in cancer and heart disease, mental disease, et cetera, et cetera.

If these cutbacks were being made by the director, as a commission we can understand that. We don't understand that this type of cutback is made by OMB.

The CHAIRMAN. So what we are saying is, we are really robbing Peter to pay Paul, so to speak. So at least in terms of research that could have important implications, in terms of cancer and other kinds of very important areas, that we are seeing some of these reductions in terms of personnel, in terms of movement into this other area.

I think that that is completely unacceptable, and I am sure the American people don't understand that, in this shell game. And it must be a matter of enormous distress; obviously it is to those who are involved in the whole research program.

Let me just finally ask you, doctor, we keep hearing about getting community physicians and organizations involved in the clinical testing. Also hearing that NIH is worried that they won't get good data from this type of initiative.

Can we do this type of research outside of the teaching hospitals? Is there a realistic way of expecting to get good quality control?

Dr. LEE. We have a difference of opinion with some of the other reports that have come out. The Institute of Medicine disagrees with us.

But I have seen community-based organizations in New York work extremely effectively. You have to realize that their boards are comprised of the top academic people in these fields.

Their trials are academically very well controlled. Personally I feel these community-based organizations have a real role to play.

Dr. Fauci I think disagrees in some way. He may want to address this when he speaks. But I would love to see this spin off into cancer research.

Senator MIKULSKI. Thank you, Mr. Chairman. I know we want to move the hearing. I just have two areas of questions.

First, Admiral, a special thanks to you and the Members of your commission for the exhaustive work that you put into this. We know that you put your time and your energy in it.

Of course we all like to applaud the news we like to hear. And of course there are accolades from someone like myself for the recommendations of the Commission.

But regardless of that, I think that what you did with your leadership and the sticktoitiveness of the commission during rocky times really showed the fact that—the Commission's report shows integrity, shows competency, and shows compassion.

And I think there is a grateful Congress and a grateful American people to you and all the people who worked so hard on it.

The area that I would just like to bring up, not to duplicate Senator Kennedy's questions, is, in your report you talk about how health care professional education process is unresponsive to the new fast-moving deceptive medical threats like HIV.

And you go into the doctors, the dentists, but you also go into the paramedics, the policemen, the firefighters, et cetera.

Could you elaborate a little bit on what you think needs to be done, and where it needs to be done? For example, we talk about the unfettering of NIH. But should we unfetter CDC? Where should that be coming from? How should it be best done? And how could we make sure that it happens?

Admiral WATKINS. Senator Mikulski, we thought it was so important, this particular health worker safety area that you are talking about, that we designated an entire Chapter 3 to health care provider information, because we thought it was one of the most neglected issues inside all the discussion we'd heard to date on AIDS.

And we listened to firefighters and policemen and paramedics, people who really work the problems day after day, even in your city of Baltimore. They are cut every night hauling people out of broken windshields. The exchange of body fluids is very highly likely, and they're given very little time.

And also volunteers. There are so many volunteers out there who really get no time of day when it comes to protection equipment and all that sort of thing.

There is no central clearinghouse, there is no repository, for all that information exchange.

It happens that in Baltimore, for example, you have some of the finest protective equipment, for some reason, and Indianapolis decries this because they say, we don't have any out here.

So this issue just cries out again for much more coordinated action; much more sensitivity to other people involved in the business.

Also, they aren't provided with the kind of real time dynamic updated scientific information on which they can base some of their own programs, their training programs, their education programs.

We don't really try to coordinate their education. We think in terms of education, unfortunately, in the schools too much. It is out of the school. It is the kids not in school that we worry about; those are the high risk kids.

It is the people not in the workplace as well as the people in the workplace.

So education, you will see in our report, is much broader than just school; thinking about whether you're going to teach about condoms in the third grade. It is far beyond that.

And we so we touch on health care providers because there is a great need. And we have made a very large number of recommendations. We made it a separate chapter.

Senator MIKULSKI. Where should this action be located?

Admiral WATKINS. CDC, you will see in there, we make some very specific recommendation, we think needs to get into all of the auxiliary or the alternate health care provider work.

It just simply doesn't exist today in any kind of coordinated fashion. It doesn't exist. But we think CDC is properly the place to put it.

Senator MIKULSKI. Did you find out why it didn't exist at CDC?

Admiral WATKINS. It just hasn't bubbled up to the top of the priority list. And I think that we have forgotten the very people who are out there slugging in the trenches everyday on this issue.

And frankly, they're getting burned out, and they're worried about it. And we've got to give them hope.

Dr. LEE. May I answer one of your questions, Senator Mikulski? The reason that we picked NIH for special treatment is that it is a university.

Senator MIKULSKI. Oh, I understand. No, I'm not saying it is either/or. But I think one of the things that emerges from the Commission's research is that there needs to be a coordinated, comprehensive approach in which every agency of government moves on this subject: NIH in its research; CDC in its mission.

Quite frankly, I think Social Security should have an administrative office to fast track applications. I think HCFA has to work at its reimbursement system.

It reimburses for acute care for some of the treatment that could be done at home. And instead, we pay for the most expensive treatment, and we won't even give a nod to other reasonable, rational, alternatives.

Admiral WATKINS. All of the things you say, Senator Mikulski, are outlined in our report, and you are right on target.

Senator MIKULSKI. We have so many other witnesses, Mr. Chairman. I think that we are moving. I am going to be going to the CDC during the Democratic Convention, at my own expense, I might add.

But we will take a look at some of those recommendations laid out there.

Thank you.

The CHAIRMAN. I too want to commend those recommendations where you outline each. And as Senator Mikulski was talking about the responsibility of the Department of Labor through OSHA; the joint commissions on accreditations of hospitals; require health care facilities to make infection control.

You go right down the various agencies in defining those responsibilities. It is enormously helpful. I think it is going to be a real guide.

Admiral WATKINS. I think this relationship in this area that we were talking about between OSHA and CDC just isn't defined. It has to be spelled out. Everybody is kind of pointing to the left.

Senator MIKULSKI. When we were working on the legislation, I specifically put in language related to the public safety officers who respond to gore and trauma.

Well, then we had all this picky little prissy debate over, should it be at OHSA or should it be at CDC. And do you need to have white lab coats to do it or can you do it in overalls, and I just wanted to do it.

Admiral WATKINS. Well, I got into trouble with my commission by drafting up a Chapter 12 to put a hammer in the whole system, and had to back off a little bit to get consensus on our final report.

But I tried to pick up on those items, say, for God's sake, let us put somebody in charge of this thing to hammer things together, bump heads. And let us move this thing in an integrated, collective way, and then we will start getting control of the epidemic.

The CHAIRMAN. I want to again commend you for the service to the country, Admiral Watkins, the other members of the panel. I think the best way that we can express our appreciation to you is

for this committee to weigh and consider and implement those recommendations.

And I think we will certainly give you the assurance that we will do everything we possibly can to do that. And I think that is the best way we can, other than to praise you and the members of the committee, that is the best way that we can show our appreciation for your service to your country.

Admiral WATKINS. That will be our greatest reward, Mr. Chairman. Thank you.

The CHAIRMAN. Thank you very much.

Our next witness, Dr. Frank Young, head of the Food and Drug Administration, the agency which decides really which drugs can be made available to these sick patients.

We welcome you, Dr. Young, and look forward to your presentation. You have a rather extensive statement. It has a lot of important material.

But we would like you, if you would, to sort of highlight so we can focus on the areas I think of greatest interest.

STATEMENT OF DR. FRANK E. YOUNG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. YOUNG. Absolutely, Mr. Chairman. If I could, I would like to introduce my panel, and then I would, with your permission, just illustrate the most important points, using a few posters, so that they can be clearly seen.

First on my far left is Dr. Burlington, who is from the Center for Biologic Evaluation and Research.

Dr. Jim Bilstad, from the Center for Drug Evaluation and Research.

On my immediate right, Dr. Jerry Quinnan, from the Center for Biologic Evaluation and Research; and Dr. Ellen Cooper, who is in charge of the drug evaluation for AIDS products in the Center for Drug Evaluation and Research.

Mr. Chairman, I first want to start out by complimenting you and Senator Hatch and other Members for holding this hearing, and for Senator Mikulski to make some site visits in our state to see the epidemic first hand.

I would like, with your permission, to move to the graphs, so I can just summarize some very important points.

The CHAIRMAN. We will include the whole statement in the record.

Dr. YOUNG. I would like to provide first an overview of the drug evaluation process. I know, Senator, that you are very familiar with this because of looking into this field over the years, but I think for others it might be very important.

The first portion, done outside of the Food and Drug Administration, is really product discovery, development, and animal testing. And it is this area that in part was discussed in the very important recommendations for research at the National Institutes of Health. Without the initial screening of drugs, and without the animal testing, the compounds absolutely will not be available.[1]

[1] See table No. 1 in prepared statement.

And the Admiral, in his very comprehensive report, and I certainly join with you in congratulating the Commission for their efforts, focused on the need, on page 39, for model systems and for sharing of resources to get this process really moving.

If one looks at the large number of compounds tested, thousands are screened before a very few come to the Food and Drug Administration (illustrated in blue here) for evaluation as to whether or not they are safe enough to go into people.

This takes about 30 days on the average. With AIDS drugs, we are turning these around in about five days, because we have been working back here with the sponsors in a very proactive way during this phase of the development.

After one moves into the clinical phase, this again is outside the FDA, other than that we try to interact as much as we can in the process. And I will go back and forth later on in other slides to phase I, where one primarily looks at safety; phase II, where one does the earlier efficacy studies; and phase III, the verification of this; and then, finally, to where the application is put together for a premarketing evaluation by the Food and Drug Administration (indicated in blue.)

Not only because of AIDS but because of other desperately ill people, we are trying to make drugs available at the end of phase II. I know your interest, and most of my discussion will be centering on this, but I wanted to give this perspective.

Now, if I could have the next chart, leaving that one up, I will try to show the increase that has occurred in INDs, and that are either in Phase I, II, or III. I am now emphasizing data both from the National Institutes of Health, which submits about 40 percent of the INDs, and from the private sector, which has submitted approximately 60 percent of the total investigational drug applications that are underway.[1]

As you can see, and as we would expect, in 1981 there were no applications related to AIDS, and one sees a marked increase after that.

We do not know when this will be levelling off, but there has been a marked increase in the number of investigational new drugs that are under study.

Again, I must emphasize that these tests are required first. And what we are seeing in this portion of the graph is really a lot of drugs that were on the shelf. They were not specifically developed for AIDS; that use is just beginning to be looked at and possibly coming into the system.

The next graph shows an analysis of the way these drug applications are distributed. Approximately 56 of the INDs are for drugs that modulate the immune system; 39 are for antivirals; 34 are for opportunistic infections; and 3 are for vaccines. We have shown the diagnostics here as well, of which there are 40.[2]

If one looks now and says, let us take the average antiviral drug or anti-opportunistic infection drug, and let us try to make a projection of what would happen to this drug in the process, these are Phases I, II, and III. We got these data by going back through 1976,

[1] See chart No. 2 in prepared statement.
[2] See chart No. 3 in prepared statement.

1977, and 1978, and projecting the fate of these drugs in 1987. So it is a retrospective study.

If one normalizes these to 100 percent, one sees that 70 percent of these drugs will remain after Phase I, most of the rest dropping out because of safety concerns.

After Phase II, 33 percent will remain, a large portion dropping out because of safety problems and efficacy concerns. We also see some dropping out because there is no commercial interest in them.

If there is no commercial interest, by and large it results in the drugs not only not being developed in the United States but nowhere in the world.

At the end of Phase III, one has 27 percent of the drugs brought through this process; again, some drop out because of safety, and 20 percent of the drugs get approved.

Now we have tried to project this and say, what might happen to all of the INDs that are now undergoing investigation for AIDS? Because people have legitimately asked, where are the drugs?

And so Paul Coppinger has developed a mathematical model. And I'm going to read the assumptions off, because the numbers that I give you really are based on the model and these assumptions.[1]

It includes all therapies for AIDS, and includes, therefore, antivirals, drugs for opportunistic infections, immunomodulators, and antineoplastic drugs, and excludes vaccines and diagnostics.

It converts the total number of AIDS INDs into distinct therapies. Currently, 33 of all of the INDs that I've shown you are distinct therapies.

It assumes, and this is the major underlying assumption, that 14 additional therapies per year will be developed. This is a 1987 rate. Could I have the projection again of the increase?

We have no way of determining what this rate will be. It may continue to go up. It may continue to change at a slightly slower rate. But we have assumed a constant rate of 14.

It assumes that AIDS therapies are more difficult, twice as difficult, to bring to the point of marketing as conventional drugs; it also assumes that the FDA approval rate will be the same as the historical rate for other conventionally more difficult categories, that is, cancer drugs.

And the model, as a total development in time—that is, IND to NDA approval—is projected based on our going twice as fast as we would with any other drug.

So it's gone twice as fast. Fourteen new therapies per year. And it is at the rate of the drugs that are most difficult to evaluate.

If one looks at these types of assumptions, now plotted against the total INDs that are available, one gets this type of analysis. And I emphasize that this is a mathematical model.

In the year 1991, there would be 320 INDs; 99 therapies under study; 6 marketing applications for distinct therapies; and 1 to 2 additional successful therapies beyond AZT.

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[1] See chart No. 4 in prepared statement.

Running these numbers forward with the same assumptions, the model projects 520 INDs; 155 therapies under study; 14 marketing applications; and 5 to 6 new drugs in 1995. In the year 2000, one sees 24 marketing applications and 9 to 11 drugs.[1]

The point to emphasize is the marked fallout during the investigational study of these AIDS drugs.

Now, what about the treatment IND, and how can we look at what has been done in the past and what might be projected into the future?

The CHAIRMAN. Before we get into that, because that is an important issue as well, I suppose a reasonable question is "Why aren't we getting more into the earlier phases in clinical trials?"

And as I remember your other comments, you get about 40 percent from the NIH. NIH, as I understand, is used also for commercial development drugs. Why aren't we getting more? Why isn't there more coming into the system?

Dr. YOUNG. I think there are two answers to your question. The first is, we're seeing a lot of the drugs that have been screened in the past. Dr. Broder at NCI has had a wonderful screening program, which gave rise to the screening of AZT.

But there are a lot of compounds being screened, and they need to get to the animal testing phase.

The CHAIRMAN. How long did that take?

Dr. YOUNG. His screening program for AZT—and Dr. Fauci may be able to give more precise information—but that took a couple of years, I believe, to do the animal studies before getting into humans. It was a very toxic drug.

So there is a lot of study that is involved in the animal work very early. That is one barrier.

Another barrier, and I think we have pretty well removed it, is how long it takes for the drug to be evaluated at the FDA. The average time for a drug going through our process was approximately 30 days in the past. We have been able to reduce this to 5 days by working with the sponsors early.

But the barrier is essentially how many drugs are tested, and how much research is going on, Senator. That really is the bottom line: how much research?

The CHAIRMAN. But the kind of research involving animals is really somewhat different, isn't it, from other types of clinical research?

Dr. YOUNG. Yes, one of the major problems that we have in this disease is a lack of good animal models. Therefore it is harder, particularly in vaccines, to be able to test these.

In the case of drugs, much of the animal testing is done here both for toxicity and for birth defects. Those are the kinds of animal studies that are done.

A lot of the drugs are first screened. If you were to take my back-of-the-envelope calculation, one starts probably with about 10,000 ideas; may screen 1,000 compounds; and may put 100 into clinical testing.

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[1] See chart No. 5 in prepared statement.

The CHAIRMAN. Well, if the animal profile has less application for this particular challenge, involving AIDS, shouldn't we be taking a look at the challenge in some different way, rather than following a "business-as-usual" way or traditional way of approaching this kind of research with the utilization of animals?

Dr. YOUNG. We've been trying to moderate this as much as we can, Senator. And by working with the sponsor in the very early animal phases, we have been able to reduce, in some instances, the amount of testing.

And by close cooperation, we were able to drop the total time evaluation for AZT to 22 months, much less than the 8 years average that it takes a drug to develop.

[Information supplied follows:]

ADDITIONAL INFORMATION ON DR. YOUNG COMMENTS

With respect to the use of animals in the development of new AIDS drugs, and the time required to conduct the preclinical animal studies, we would like to provide some additional information to expand upon the comments of Dr. Young.

As Dr. Young mentioned, we have been able to greatly reduce the review time for new AIDS drugs by closely interacting with drug developers very early in their research and development program. Through this interaction we are able to help the sponsors identify those essential studies necessary to describe the potential toxicity of the new drug so that safe clinical studies can be designed that minimize the risk to the patient. New drugs are able to enter the clinic quickly because the necessary animal studies are usually only 4 weeks long, and sometimes shorter. For example, the preclinical animal studies completed before initial human use of AZT were only 2 to 4 weeks long, and the most recent new AIDS drug from NCI entered the clinic after only 2-week animal studies. The variations exist because each new drug represents a unique set of circumstances for which the preclinical studies are customized.

In each instance, by working closely with the sponsor we have tried to reduce the amount of preclinical testing without compromising the safety of the patient. Unnecessary studies are avoided, and the company is able to more efficiently allocate its time and resources to get the drug into the clinic in the shortest amount of time.

There is also a need for animal models of the disease to rapidly screen potentially useful drugs from the thousands of new test chemicals being synthesized by drug developers. Unfortunately, good animal models for AIDS are not yet developed to quickly identify the most promising drugs. We rely almost entirely on cell culture studies that are fast but imprecise and may miss identifying the best drugs. FDA is not directly involved in the development of new animal models, but tries to coordinate universal use of new methods among drug developers as they become available. This is another aspect of our early interaction with the sponsors and should result in more promising drugs to study in the clinic.

The CHAIRMAN. Well, again, I would just come back to the question, if you have more limited utilization of animal research in terms of coming to grips with trying to look at new prospects, is it legitimate to think that you ought to be able to use a different kind of profile and use human beings that are going to be carefully supervised with a more effective post-marketing kind of situation on them?

If that is the situation, I understand it to be the situation, then why the devil aren't we trying to develop a different kind of a profile, to move additional kinds of compounds into these types of preclinical tests?

Dr. YOUNG. You are correct that there is some limitation. It is not a great one. But in the fields of vaccines, as you know, I was publicly criticized tremendously for going right to people without animal studies on that.

But the agency did that because we felt, just as you said, that in certain instances that it should be possible to bypass some of the studies and go directly to humans.

The CHAIRMAN. What is the state of the decision-making process over in FDA now on that issue?

Dr. YOUNG. Most of this is really done on the part of the sponsor. They bring to us——

The CHAIRMAN. But what about NIH? They bring a substantial number of those, about 40 percent you indicated. What are they doing on it?

Dr. YOUNG. To the best of my knowledge, they are doing the animal testing that is appropriate to remove from consideration those drugs that would be highly toxic. Dr. Fauci can speak to that more directly.

The CHAIRMAN. Okay, let us get to your other material.

Dr. YOUNG. Right. The caveat here is that we do not require the essential things in the same way as Phase I, Phase II, Phase III. We only look at safety going through.

And I should say, Senator, probably about 87 percent of the drugs have been quite rapidly approved; about 5 to, at the most, 30 days turn around time, where there had been no studies at all in animals. And there are some limitations there.

Your point is very correct, because what goes into the pipeline in part is going to determine what comes out at the other end. And the point that I wanted to make very clearly here is that this is a complicated process, and many of the drugs are going to fail; with AIDS drugs, probably 90 to 95 percent will fail because of a lack of safety or a lack of effectiveness. It is going to be a difficult task.

The CHAIRMAN. Well, I think as well, what goes into the pipeline, and whether it will be too restrictive in terms of getting into the pipeline, I think is an issue.

But let's go to this other point that you were bringing up.

Dr. YOUNG. Right, I wanted to go the treatment IND. One of my concerns, when I came to Washington, was to try to make drugs more available to desperately ill people. And, as you know, I have put a lot of emphasis on this particular regulation.

We have plotted on this panel the average number of patients studied prior to approval of an NDA. As you can see in Phase I, there are about 10 to 50 people studied for safety.[1]

One then moves into the Phase II trials, and the trials vary, but anywhere between 50 and 200 patients are studied on the average. 200 to 1,000 or somewhat more are studied in Phase III.

Five treatment INDs have been approved to date. The first one, which was from the State of Massachusetts, for an antibody for CMV infections in renal transplant patients, required a total of 60 people. This constituted the base on which safety and effectiveness for that product were decided.

In the case of the solid testicular tumor drug, 59 patients constituted the total base that was studied, in contrast to thousands for other products.

In the case of trimetrexate, 73 patients were in that particular study.

The other two drugs were much closer to marketing. In case of the anafranil, there were 740 patients; in that case, the drug was under investigation for a number of years.

And in the most recent approved drug for Parkinson's disorder, 540 patients were studied.

We anticipate, for the AIDS-related drugs, that we will be approving drugs for treatment INDs with a much lower number of patients.

The CHAIRMAN. With respect to DHPG, you do agree it is effective?

Dr. YOUNG. DHPG has been studied for a period of time. We have some indications that it is effective, but we have not been able to get the solid evidence.

We have had those studies done under clinical compassionate INDs. That has been a problem in that particular case.

The CHAIRMAN. Well, what do you use on post-marketing? Do you use any of the post-marketing surveillance?

Dr. YOUNG. Yes, we do.

The CHAIRMAN. Would it be useful in this situation where you get it out and then do a monitoring and a review so that you would be able to get additional kinds of both scientific and clinical information that would be valuable?

Dr. YOUNG. To the best of my knowledge, the difficulty that we have is writing a summary basis of approval for this. We have looked very hard at it, and I have reviewed the data myself, but not in the depth that Dr. Ellen Cooper has, and I would ask her to comment in just a moment.

But the difficulty that we have is that we have put it under a compassionate IND. We have been able to get a lot of information and the drug is widely available. It is not restricted because of its use and availability under a compassionate IND.

We are going to convert it, we hope in the not-too-distant-future, to a treatment IND. But Dr. Cooper, could you comment on that?

The CHAIRMAN. I would be interested in hearing that. But just for the record, the real way you get it out to distributors is through

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[1] See chart No. 6 in prepared statement.

marketing, I mean, even with the availability of the compassionate IND. The real way that these get out is with a distribution and commercial marketing.

But we could hear from the doctor.

Dr. COOPER. I think one of the problems that to some extent has inhibited the development of controlled trials with this drug is that it was made widely available before controlled trials were done, and so it has been very difficult to gather the information to demonstrate in a variety of infections caused by CMV that the drug has efficacy as well as safety. And we have been working with the sponsor, and controlled trials are about to go forward, sponsored by both NIH and the manufacturer.

In the meantime, the drug is still available to patients with CMV retinitis.

It has been a very difficult case study, a very difficult drug in the whole development process.

[Information supplied follows:]

INFORMATION ON THE NEW DRUG APPLICATION (NDA) FOR GANCICOVIR (DHPG) FOR THE TREATMENT OF CYTOMEGALOVIRUS (CMV) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

The New Drug Application (NDA) for ganciclovir (DHPG) for the treatment of cytomegalovirus (CMV) infections in immunocompromised patients, and more specifically, CMV retinitis in AIDS patients, has not been approved by the Food and Drug Administration because the data submitted by the company in the NDA were insufficient to demonstrate effectiveness and safety.

FDA must base its decisions regarding the approvability of a new drug on the evidence submitted by the sponsor in support of the safety and efficacy of the product for its intended use (indication). In the NDA for ganciclovir, the clinical data were obtained from many individual physicians around the country who had treated patients under a large "compassionate use" program begun in 1985 under which the drug was made widely available before controlled studies, designed to demonstrate the safety and efficacy of the drug, were performed. Such a "compassionate use" program results in data that are difficult or impossible to interpret with any confidence.

This does not necessarily mean that the drug does not work; it does mean, however, that the data submitted do not demonstrate that it does work. In addition, ganciclovir is a toxic drug, toxicity which is acceptable in the face of clear benefit to patients with sight or life-threatening infections, but unacceptable in conditions for which efficacy has not been demonstrated. FDA is working with both the manufacturer and the National Institutes of Health to help expedite the design and implementation of well-designed, controlled studies in CMV retinitis in AIDS patients and for other indications.

FDA is also working with the manufacturer and the National Institute of Allergy and Infectious Diseases with regard to the implementation of a ganciclovir Treatment IND for the therapy of sight-threatening CMV retinitis in patients with AIDS.

The CHAIRMAN. Well, the fact is, as I understand it, it has been effective in preventing people from going blind, is it not?

Dr. COOPER. Many physicians who have treated patients with retinitis would certainly——

The CHAIRMAN. Well, I think there is certainly a strong case that could be made for that. And with all respect to the compassionate use, to require people to weave their way through that kind of a maze, to be able to receive it, you're balancing that versus the question of where you are getting it out; you're getting reports from the company; doing that kind of review.

Perhaps in many of these instances, you are saving people's sight. And again, we want to stress and emphasize the importance of scientific information, and not getting things out rapidly that aren't effective and certainly safe.

But you have got, certainly, the kind of crisis situation that you have here. And I think it does put a very, very heavy responsibility in making sure that things which have—are demonstrating to be effective, it is going to be an important responsibility in getting these out, and finding new ways of trying to get them out, and then to monitor them.

It seems to me that you have got this unique circumstance where most of these compounds impact the people, and the profile use of animal, which might have been important at other times, perhaps relevant in some areas here, less relevant in many different areas.

And the only way you're going to be able to do it is to get it out and get it into people. So many of whom are quite glad to be willing to be involved in this process. And then to monitor and to monitor it closely.

Dr. YOUNG. Senator, I want to return to your point, because you have a very important idea, and I saw it in your 1979 bill.

Our problem is, in part, a legislative one. I raised this with the company when we met with them on a couple of occasions.

We cannot, under our current authority, require a Phase IV study. I also brought this up to the Admiral and the Commission as a potential weakness in our current legislative capabilities.

If we were able to require appropriate Phase IV studies, we might be able to do, with much more confidence, the type of evaluations that you're thinking about.

And also, if it was——

The CHAIRMAN. Are you suggesting you need additional—as I understand you're doing some post-marketing in any event on AZT?

Dr. YOUNG. Yes, but they are voluntary agreements. We do not have the authority——

The CHAIRMAN. Have you tried voluntary agreements with others?

Dr. YOUNG. We have tried some, and we have had some succeed while others have failed.

The CHAIRMAN. Well, I would just welcome legislative changes in this area. I'm a strong believer in that post-marketing surveillance. I think it is taking place in other countries of the world, working effectively, getting other kinds of drugs out much more rapidly.

And if you need it in terms of this particular area, I just can't believe that it would take longer than an afternoon to get it through the Senate.

Dr. YOUNG. Well, you know that I have been a user of post-market surveillance extensively since I've been in the agency. We have done that with lovastatin and a number of other drugs.

We debated a great deal about whether it would be possible here. But because of the equivocal nature of the data and the difficulty in getting a mandatory Phase IV study, we did back away from it and went with the treatment IND approach.

The CHAIRMAN. Let me just go back in terms of the treatment IND. Now, I'm not a physician or a scientist, but I want a reading that there is confusion out there about the criterion that is going to be applied by the FDA in deciding whether to release a drug under the treatment IND.

Is the standard that a drug may be effective, or must there actually be some kind of documented evidence that it is effective?

Dr. YOUNG. Evidence is required that the drug shows some degree of effectiveness; that it may be effective. There has to be, by this definition, some degree of effectiveness.

The CHAIRMAN. Has it got to be more than a shred of evidence?

Dr. YOUNG. Well, let me try to put it in the form of the whole drug evaluation system.

The CHAIRMAN. Well, I want to hear that. But I want to also get what the standard is. Could it actually be approved under the treatment IND before it goes into Phase III trials?

Dr. YOUNG. Yes, it could.

The CHAIRMAN. You are very much aware of the various reports that were made. You know, you made a lot of comments. A lot of hopes were created. There was a lot of cynicism and skepticism and frustration as I'm sure you are aware now.

Dr. YOUNG. Yes, I am.

The CHAIRMAN. And part of this whole process of these hearings is to try and clear up the ambiguities. And I am worried that there may be mixed messages going to those terminally ill patients who are clearly under the impression that the regs were considerably loosened last year for getting these experimental drugs out to them.

And I am sure you have heard that they feel let down, not actually misled. Would you care to set the record straight about just what they can expect from this program?

Dr. YOUNG. Surely. We have received a total of four treatment IND applications. One was for ribavirin. This was turned down; the drug did not have, in our opinion, as we have testified in other settings, the efficacy that would be required.

One was for trimetrexate, which was approved. Two were from the same investigator, and an IND had not even been filed. It just came in as a treatment IND with an idea; with no animal studies done, no patients entered in, and no chemical analyses done of a sufficient nature.

We will not know what the outcomes will be exactly, or the timeframe, since trials are not open. Our dilemma is that we cannot approve something that we do not have the application for.

And that's been something that I have said over and over again. And we made these calculations to point out that there is not a great deal in the pipeline at this immediate moment.

The CHAIRMAN. Well, let me go back then. From my communication with various drug companies, they believe the standard is that you have to have hard evidence.

The question is, to a great extent, what message you send out. And if their perception is that you have to have hard evidence, then you may get less than those that indicate that there's a standard that's somewhat less that you're willing to take a look at.

And I think that's the question, of whether you are going to stimulate the companies to try to move ahead, or they're going to say, this thing is going to be closed.

We have got something that may be hopeful. We want to fast track it. It may offer some opportunities. It is interesting in what we're finding out about it.

But we are not going to send that in because of what Dr. Young is saying about what the standard is going to be. So you have got to really, I think, clear that up so the companies understand, we understand, and the medical profession understands.

Dr. YOUNG. Let me say this as clearly as I can, Senator, and if I need to explain it further, please ask another question.

If one would say that at this phase, we're going to have the normal amount of effectiveness data in, and the normal amount of safety data in, at the time that we would have a treatment IND, one would not have anywhere near the amount of effectiveness data that is required at this stage.

There must be some indication that it is going to be effective. That was the battle that was fought when the regulation went forward.

As you remember, the regulation that was roundly criticized by both Congress and the scientific community was that we have even a shred of effectiveness. The first proposal came out, no effectiveness at all. And as we looked at it, it was deemed, from participatory analysis, both within the agency, without, and in the community as we developed it, that it should have a modicum of effectiveness.

I can't tell any sponsor exactly how much that will be. That will depend on the drug, the number of patients studied, and how good the study is. But I must say that it is not nearly the volume of patients studied that it is, in the case of this diagram here, at the end of Phase II; in Phase III. I believe that we are dealing with some effectiveness data, and enough data to indicate that the drug is promising, but certainly not the amount of effectiveness information that we're looking at here. Not in any way the same demonstration of effectiveness.

I cannot give a percentage, because it will vary with the drug.

The CHAIRMAN. Well, do you think we oversold this?

Dr. YOUNG. No, I don't. I don't think we oversold it, because we're looking at a regulation that is one year old. The total number of drugs coming through the Food and Drug Administration that are new molecular entities, which would be the ones that we would expect to go into this group, is about 22 per year. About half of those, around 11 to 12, are what we would call the 1A, 1AA, and 1B, those drugs that are a significant improvement. So we are looking at a total of 11 as the number that we would expect to come out per year.

In the first year of this new process, we see approximately five coming out of the organization. I think that a startup of five is a decent development.

I believe there has been confusion. There has not been as much clarity in the communication of this. And I am afraid that it looked as if there would be more effective drugs in the pipeline. But the demonstration of the number of effective therapies that are likely to come out indicates that many of those that look initially promising are not here.

Rock Hudson went to France to get HPA-23, as did other people. That drug is not looked at now as a promising drug.

The same is true with vramin. Most of these drugs are going to drop by the wayside before we get to the end of Phase II. That's the problem.

The CHAIRMAN. All right, now as I understand it, you used the word, may be effective. Some evidence that the drug is effective.

Dr. YOUNG. That's correct.

The CHAIRMAN. And I think that that is important that that message get out, since there has been some confusion. And I hope that you might be able to do that.

Now my staff is being told by some of the companies that the treatment IND will speed up release of drugs by a maximum of six to 12 months. You're on record as saying the treatment IND will cut two to three years in getting treatments out there.

Which is it?

Dr. YOUNG. If you look at the statistical analysis of this, this is now an eight-year process. Two years of that eight years are in the review by FDA; actually, on balance, the average drug takes two years to go through.

If you were to assume that you had a Phase III process which took approximately a year, and if you assume that the evaluation process were to take on the average two years, then you would be saving three years off an eight-year process.

On the other hand, the faster the drug goes through the process, the less time is going to be spent. But, on average, it looks like you're cutting off about 25 percent of the total time that it takes to bring a drug to people.

The CHAIRMAN. Well, as I understand, you have a total monitoring program in Phase III, do you, on the AIDS?

Dr. YOUNG. We work very closely with the sponsors on that, and we interact with them. But until the study is open, we don't have the data.

The CHAIRMAN. Well, we will obviously be working closely and watching this whole process closely.

Let me get back to another point. I don't want to take a lot of time on it; maybe we can submit some of this. And that is, about the resources for the FDA.

As you know, in years past, I have been a strong supporter in getting expanded resources. I think it is shameful that we have an expectation about the agency, and then we don't provide the resources and we don't give you the other kinds of support.

I haven't got my little administrative confidential note on FDA, and what you've requested, and what OMB did to you. But if some-

one in that shop wants to throw it through my transom some night, we would be glad to get it.

But seriously, what comment would you want to make on that in terms of the needs of the agency? If you didn't have an OMB looking over your shoulder, what could you tell us?

Dr. YOUNG. Well, we didn't use brown bags and drop off as many confidential documents. But there are two things that should be said.

First, in the last year, we were able to obtain the number of FTEs that were required, and that we requested for the process. That has not been true in earlier years.

We also are faced with a grave problem in the space to put people. Ellen Cooper has been excellent in recruiting for her division; that's been the good news.

The bad news is, we haven't had very much place to put the people that she's recruited, and we have crowded out other functions. We have a space problem, and if, as I've testified before, one can obtain the space for people only after the space is there, that's a danger.

The second point is that in our case, we really have to react much more to emergencies. Only two percent of our budget is extramural research, so that when we're faced with a problem, as we are now with the Senate looking at reducing the President's budget by two percent, that does cut our next year's funding substantially.

That's something that the Senate could address if they were interested, because the President's budget is not being met for the Food and Drug Administration.

The other part is in the case of emergencies. We are responsible for things such as the quality of assurance of condoms and the quality of the blood supply. And if at any particular year, we deem that we need to increase the number of inspections because of problems with products in the marketplace, your Phase IV surveillance, we have no way that we can easily meet those needs, and really to respond.

We have to do it really by cutting down other programs. That has been a problem.

And finally, we need to do some applied research with regard to looking at ways in which we could speed a product through the system. For example, dextran sulfate is a drug that is of great interest now. It is not known how much is absorbed, and it is not known how much can be pharmacologically active. We have diverted, without additional funds, a small amount of money to Dr. Peck so that we can start looking at this, and look at plasma levels, so that we can determine as fast as we can whether this is likely to be a good lead; and so that we can give advice.

These kinds of research, applied to national needs, are very different from the NIH mission. NIH is really the custodian of fundamental research. These are areas that I think we need to be able to address. A small amount of money on the margin would enable us to work with sponsors and do some critical testing.

So it comes down, really, to the right number of people. We are falling behind in this. The applications are outstripping the number of people, and I have said that repeatedly. The space and the research and the emergency funding.

The CHAIRMAN. Well, we thank you, Dr. Young and your colleagues here.

I think all Americans know or should know how enormously important your agency is in terms of the availability of drugs, and in terms of this whole battle, the battle on AIDS.

And I think the spirit which you heard here across the board, Republican and Democrat, is, we want you to have the resources; we want you to have the personnel; we want you to have the space; and that's something that we have to work out.

And we hope that you will let us know, because we want to support that. But we also expect that we are not going to have the business as usual.

I know that is not your own attitude, and I'm sure that it's a heavy burden on many of the professional people there in the agency.

But we have to be able to work together on this, getting you the resources, giving you the support, but also, ensuring that we are going to be able to get the extra effort and focus and attention on what is not only a national epidemic but a world crisis.

And I think your agency literally holds in its hands, in many respects, the lives of so many hundreds of thousands, potentially millions, of American citizens. So it is an extraordinary responsibility. And we have every intention of working with you when we can work together, and also to point up areas where we believe that there can be further action.

We want to thank you and your colleagues very much.

Dr. YOUNG. Thank you very much, Senator. I appreciate your support, and I want to promise you that it won't be business as usual. This is something that we are very, very concerned about.

The CHAIRMAN. Thank you very much.

[The prepared statement of Dr. Young and the information referred to on page 22, line 7, of his statement follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

FRANK E. YOUNG, M.D., PH.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

JULY 13, 1988

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I am pleased to be here today to discuss with the Committee the Food and Drug Administration's (FDA) activities related to the testing and approval of new drugs and vaccines to treat and prevent the spread of AIDS. Several of our experts are also available so that we can respond to any specific questions you may have.

First and foremost, let me say that we are most concerned about the individuals who are suffering from this devastating disease and are painfully aware of their desperate efforts to seek treatment. No higher priority exists for us than to find a way to alleviate their suffering and provide hope for those infected with this deadly virus. But I would like to note that clearly this is too big a problem for any one Agency of Government, or indeed the Government by itself, to handle. Although the Department of Health and Human Services, through the Public Health Service (PHS), has done a remarkable job of coordinating and supporting the efforts of its component agencies in the fight against AIDS, we also need the help of the private sector.

With regard to the development of new AIDS therapies, there must be close coordination between FDA and the National Institutes of Health, as well as industry and the research community. NIH has the lead responsibility for AIDS-related biomedical research and FDA staff are also actively involved in several research endeavors. FDA and NIH are working closely to facilitate the development and evaluation of any therapeutic agent which appears to be promising. These efforts are

directed toward the screening and testing of antiviral products, products which will stimulate the immune response, and products which will be effective in the treatment of the opportunistic infections associated with AIDS, and the development of a vaccine against the AIDS virus.

As you know, FDA's primary role in combatting AIDS is based on our responsibility to oversee the testing of new AIDS-related products and the eventual approval of those that prove safe and effective.

To ensure that those products, once developed, reach AIDS patients as rapidly as possible, we have instituted significant new procedures at FDA for reviewing AIDS drugs, making it our highest priority to provide the most timely and efficient premarketing review possible for promising new AIDS therapies. I assure you that we will modify our regulatory procedures to contribute in any way possible, consistent with our responsibilities under the law, to winning this war, while still assuring the safety and effectiveness of the products we regulate.

We have also formalized procedures for making investigational drugs more widely available to those who are desperately ill and reorganized our drug and biological review offices to concentrate our efforts better on AIDS therapies. We have approved for human testing the first two HIV vaccines and, approved for marketing, the first drug for the treatment of AIDS, AZT, in record time, and approved the first AIDS-related treatment IND (for trimetrexate) under our new regulation for making

potentially beneficial investigational drugs more widely available. In developing this treatment IND we worked closely with Dr. Fauci at the National Institute of Allergy and Infectious Diseases. We are directing much of our research and advisory resources towards active assistance of potentially effective AIDS drugs in order to expedite development of successful manufacturing, biopharmaceutical and clinical trial standards.

FDA'S RESPONSIBILITIES AND ORGANIZATION

To assure that AIDS products get the highest priority and to give increased attention to the drug evaluation process in general, we have within the past year implemented a number of management initiatives. First, last fall we divided FDA's Center for Drugs and Biologics into two new centers--the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). I have also consolidated the coordination of all of FDA's AIDS-related activities under Dr. Paul Parkman, the Director of CBER and a highly regarded expert in viral diseases, to ensure that AIDS-related issues are properly coordinated throughout the Agency and with the PHS.

CDER, under the leadership of Dr. Carl Peck and with the aid of CDER's AIDS coordinator Dr. James Bilstad, is responsible for the review of most new AIDS drugs. In fact, within that Center, we have recently created a new Division of Anti-Viral Drugs with special laboratory resources specifically to concentrate on expediting review of potential

antiviral and other anti-infective therapies being developed to combat AIDS.

CBER is responsible, in general, for issues related to the safety of the blood supply and for the review of new vaccines, blood products, AIDS diagnostic kits, and biological drugs (primarily cytokines, which interact with the immune system, and monoclonal antibodies). To manage better the review of new AIDS biologicals expected to result from developments in biotechnology, we have also established within that Center a new Division of Cytokine Biology which will contain several laboratories capable of in-depth study of cell biology, immunology, and other possible keys to understanding this deadly virus.

The dramatic expansion of CBER's AIDS-related activities has resulted in the need for additional facilities for its regulatory function. The regulation of biological products involves the performance of applied and product-related research by the same scientists who review IND submissions and license applications for biologics. To meet this need there is included in the 1989 budget funding for construction of a new building on the campus of the National Institutes of Health. This building will be adjacent to the other CBER buildings and will house our regulatory scientists working on AIDS.

Finally, we have been increasing our inspectional activities to ensure that the scientific data on all new drug and biologic product applications are of high quality. This will assure that products made for use in research are in compliance with our Good Manufacturing

Practice regulations and that studies are conducted in accordance with our Good Laboratory Practice and other applicable regulations.

I want to emphasize that FDA has realized a significant increase in personnel in recent years for AIDS-related activities. In addition, the President's 1989 AIDS request of 254 FTEs in 1989 represents almost triple the number of FTEs devoted to AIDS since 1987, when 90 FTEs were committed to this effort.

Despite all our efforts it is no easy task to develop new AIDS therapies. We are dealing with an extremely complex etiologic agent in the HIV, and under the best of circumstances only a small number of approved products will result from the many Investigational New Drug Applications which are submitted to FDA because of problems with safety and effectiveness observed by the sponsor during clinical trials. In addition, the special circumstances of AIDS may make it more difficult to conduct adequatedly controlled clinical investigations. I will discuss these issues in more detail later in my testimony. However, I want to assure you that we are committed to working with both the public and private sectors to make every effort to find effective therapies.

PREMARKET DRUG REVIEW PROCESS

Before describing the progress FDA has made in the AIDS area, let me remind you how the premarket review process operates and then discuss how we have modified our procedures to help people who are desperately ill with AIDS. In order for clinical testing to proceed with products

intended for use in the treatment of AIDS (or any other condition), an Investigational New Drug (IND) application is filed with FDA. The IND must contain information adequate to demonstrate that it is safe to test the drug in human subjects, and includes drug composition, manufacturing and control data, results of animal testing, training and experience of investigators, and a plan for clinical investigation. In addition, assurance of informed consent and protection of the rights and safety of human subjects is required. This process is normally accomplished in 30 days with 95 percent of non-AIDS INDs but, because of our close coordination with sponsors, studies for AIDS drugs generally have been allowed to proceed in just 5 days.

For drugs in general, clinical testing, whether done by the pharmaceutical company, an academic institution, or the National Institutes of Health, is normally divided into three sequential phases. Phase I is the initial introduction of an investigational therapy into humans to determine safety. Phase I studies are intended to assess the safety of the drug carefully with an emphasis on evaluation of toxic manifestations of the therapy, how the body distributes and degrades the drug, and side effects associated with varying doses. Phase I often includes fewer than 100 normal volunteers or patients and may take one to two years to complete.

The second phase is the first controlled clinical study in ill patients to evaluate the effectiveness of the drug for a particular indication and to determine common short-term side effects. A Phase II study typically involves a few hundred patients. It should be noted that most

drugs that fail in the IND stage do so in Phases I and II. In fact, 90 percent of these drugs are abandoned before reaching Phase III mainly because of excessive toxicity or inadequate benefit.

Once a Phase II study is completed, the drug's sponsor has learned much about the drug's safety and effectiveness, and a larger controlled study using several thousand patients--Phase III--can be conducted. This large study is primarily to verify the initial studies and to collect enough information to prove that a drug really works and can be marketed safely. Although FDA strongly encourages sponsors to work closely with the Agency in planning definitive Phase III clinical trials so as to ensure adequacy of clinical trial design, many do not avail themselves of this valuable opportunity.

Once Phase III testing is completed, the sponsor submits the test results to FDA in the form of a New Drug Application (NDA) or product license application. FDA's medical officers, chemists, statisticians, and pharmacologists review the application in parallel to determine if the sponsor's data in fact show that the drug is safe and effective. Of the eight years that are typically devoted to the clinical study of drugs by the sponsor, about two years are required to review non-AIDS drugs.

To make this process more efficient, and to reduce this time, FDA has recently completed an extensive reform of the regulations governing the drug review process and is recruiting additional reviewers. The new regulations are intended to simplify and expedite the testing and application review phases of new drug development. Concomitant with

those new regulations we have issued guidelines to help sponsors better plan their clinical testing and to encourage careful planning between FDA and sponsors--to ensure that testing will fully meet FDA's needs for safety and efficacy data.

PROGRESS IN AIDS TO DATE

As I stated earlier in my testimony, we have already made significant progress in assuring that FDA does its part in fighting AIDS so that potential AIDS products reach the patients who so desperately need them. Let me describe in more detail some of our accomplishments thus far.

Drug Review

A special classification, known as "1-AA," was established in September 1986 for all AIDS drugs, to ensure that they receive the highest priority in the drug review process.

Specifically, FDA has expedited the handling of all requests for the study of experimental agents for this condition. We have been available to meet with manufacturers who have expressed an interest in submitting an IND for the use of a product for AIDS or AIDS-related complex to discuss the procedures for filing an IND. In some instances, the reviewing divisions and/or the Commissioner have initiated contact with manufacturers who have a drug that shows some activity in the laboratory against AIDS, to offer our assistance in guiding them through the drug development process. We have also offered our assistance in expediting

and facilitating the filings of INDs to foreign as well as domestic firms.

In these meetings with company officials, FDA scientists have discussed the information necessary for inclusion in an IND request. They have also assisted in the design of clinical plans so that studies on drugs which might prove to be useful therapeutic modalities for AIDS could be initiated rapidly once the IND is filed. We have also initiated research in our own laboratories to expedite development of manufacturing and biopharmaceutical information and standards.

I must emphasize that the development of potentially promising new products results from the cooperation between FDA and our sister Public Health Service agencies, industry, and the bioresearch community and a willingness to share confidential data and information under circumstances which do not usually exist at this stage of drug development. This is particularly true with regard to the sharing of procedures and tests by the private sector.

With this joint effort between FDA, NIH, private-sector manufacturers, and academic scientists, approval for a newly filed IND can be granted in a matter of days, and amendments to the original protocol can be agreed to by telephone as all parties work together closely to monitor the progress of patients under study.

With regard to NDAs, the first drug for AIDS reviewed under our new priority classification--AZT (now known as zidovudine)--received FDA

approval in record time (3 1/2 months). This timeliness stands in sharp contrast to the 2 years or more the average new chemical entity spends in the NDA review process. This was not accomplished easily. To provide such an expeditious review, FDA staff worked into the night and during weekends, expending 8 person-years of effort, through the effort of 75 people working a total of 16,000 hours, at a cost of $600,000, to review a new drug application 20 linear feet tall.

Let me now provide you with some current statistics. As of June, FDA had received 209 IND's to test 140 new AIDS drugs, diagnostics and vaccines, and had allowed 85 percent (178) of those applications to proceed. As illustrated by the attached charts, the approved applications for human testing include:

-- 39 for antiviral drugs
-- 6 for antineoplastics
-- 40 for diagnostics
-- 3 for AIDS vaccines
-- 56 for immunomodulators
-- 34 for drugs for opportunistic infections

Of the 138 drugs and vaccines mentioned above, 34 percent are in Phase I, 59 percent are in Phase II and only 7 percent are in Phase III.

Furthermore, the number of these applications has been increasing markedly. It is important to point out, however, that since approximately 93 percent of these investigations are still in Phases I and II of clinical testing, we know little of their true safety and efficacy.

However, I must interject a word of caution--the vast majority of these INDs will fail to reach FDA as NDAs due to problems with safety or the failure to be effective. Our statistical projections show that the sponsor's success rate will be very low. Therefore, very few AIDS therapies will be available in the future. We have based our projections on the following assumptions:

-- that the total number of current INDs translates to 63 distinct therapies (this does not include vaccines or diagnostics);
-- that last year's pace of 14 additional distinct therapies continues in future years;
-- that AIDS therapies are at least twice as difficult as conventional therapies to bring to the point of a marketing application;
-- that the NDA approval rate is the same as for more difficult drug categories, such as oncological products; and
-- that the total development time (IND to NDA approval) will be twice as fast as that for conventional drug therapies.

I must emphasize that this model cannot predict the exact number of therapies that will be approved, but I think it is useful in calibrating our expectations in light of historical experiences with drug development in other therapeutic areas.

As shown by the attached chart, by 1991, of the 320 projected INDs for AIDS products, we project that one to two will result in successful therapies, by 1995, 520 applications would result in five to six

products and by the year 2000, nine to eleven products would come from 720 application's.

Before going on, I would like to comment on one of the experimental products which has been the subject of a great deal of publicity, dextran sulfate. Specifically, a single Phase I dose-escalation study has been conducted with this drug under the sponsorship of the manufacturer. A major impediment to more rapid development of this drug has been the lack of availability of an assay to measure the drug's levels in body fluids. Subsequent to an FDA initiated teleconference with the sponsor in April, the Office of Research Resources in the Agency's Center for Drug Evaluation and Research began aggressively developing such an assay and is pursuing collaborative pharmacokinetic studies to test this assay in both animals and humans. We are hopeful that these data will provide a sound basis for the implementation of controlled Phase II trials to demonstrate the safety and efficacy of this drug at various stages of HIV infection. This exemplifies the type of effort that FDA is expending to catalyze the development of AIDS therapies.

Treatment INDS

Mr. Chairman, you specifically requested that I elaborate on our treatment IND regulations. There are times when a new experimental drug holds the promise of hope for desperately ill patients--such as AIDS patients. In those cases, it seems imperative that we allow such patients access to those drugs once a reasonable body of safety and efficacy data exists. Although FDA has for years permitted some

patients access to such drugs, last year we concluded that a formal provision should be written into FDA's regulations permitting expanded use of experimental drugs. These so-called "treatment INDs" will allow broader use during the second phase of clinical testing of drugs for immediately life-threatening diseases. We have developed the following criteria for determining whether a treatment IND is appropriate for particular drugs:

(1) the drug is intended to treat a serious or immediately life-threatening disease;

(2) there is no comparable or satisfactory alternative or other therapy to treat that stage of the disease in the intended population;

(3) the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and

(4) the sponsor for the controlled clinical trial is actively pursuing marketing approval of the investigational drug.

For drugs intended to treat an immediately life-threatening disease, a request may be denied for treatment use if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population, or (2) would not expose patients who

receive the drug to an unreasonable and significant additional risk of illness or injury.

The drug AZT served as the model for these new regulations, when over 4,000 patients received the drug prior to formal marketing approval. It should be noted that demonstrable efficacy was crucial because of the significant toxicity of AZT. Without the observed benefit of AZT, the drug would have presented an unacceptable risk/benefit assessment and, therefore, would not have been made so widely available to patients as rapidly.

And, as I mentioned earlier, we have now approved the drug trimetrexate under a treatment IND for a narrowly defined patient population, AIDS patients with Pneumocystis carinii pneumonia (PCP) who cannot take approved therapies because of serious and life-threatening toxicities. The two therapies which are currently approved for PCP are trimethoprim/sulfamethoxazole and parenteral pentamidine. Studies are also underway in a subgroup of this patient population who are not intolerant to standard therapy, comparing the safety and efficacy of trimetrexate in combination with leucovorin to currently approved therapies. In addition, two separate studies are underway for patients who are unresponsive to standard therapy; this trial will evaluate the efficacy and safety of trimetrexate/leucovorin when compared to the alternative standard treatment in this subpopulation of patients.
We are committed to this policy of bringing breakthrough drugs to desperately ill patients as rapidly as possible. Since the regulation was promulgated, we have also approved four other drugs under treatment

INDs--cytomegalovirus immune globulin for infections in renal transplant patients; clomipramine for a severe form of obsessive-compulsive disorder; Eldepryl for Parkinson's disease; and a combination of ifosfamide and Mesna for a form of cancer (see attached chart). Additionally, we have allowed the administration of the drug ganciclovir--for CMV Retinitis--to 1,500 AIDS patients on a "compassionate IND" basis.

We recognize that many question why there are not more products under treatment IND. I would like to attempt to provide some perspective on this as it relates to AIDS, and why we have received only four applications for AIDS treatment INDS. Three of the four requests were denied either because the available scientific evidence did not provide a reasonable basis that the drug would be effective for its intended patient population or because the applications were deficient in that they contained no results of clinical studies, no protocol, no preclinical animal data and no manufacturing and controls information. We are currently working with another manufacturer on the submission of a fifth application.

I would start by reiterating that HIV is an extremely complex etiologic agent. This virus has demonstrated that it has many faces and, consequently, has confounded our search for effective treatment. Indeed, finding effective drugs against <u>any</u> viral illness is extraordinarily difficult, in large part because of the very nature of viral replication which occurs inside the cells of the infected host using cellular enzymes redirected by viral genes to manufacture viral

proteins. One statistic powerfully illustrates the difficulty of successfully developing safe and effective antiviral compounds: to date, hundreds of antibacterial agents have been discovered, to cure virtually any bacterial infection; yet, in all our years of experimentation, only seven antiviral agents ever reached the stage where safety and efficacy are known.

Not only is it intrinsically difficult to develop safe and effective antiviral agents, but disturbing signs indicate that it may become substantially more difficult to conduct adequately controlled clinical investigations for any AIDS-related drug, whether antiviral, immunomodulatory or other anti-infective. There is increasing and vocal insistence by many persons infected with HIV for immediate, early access to new experimental agents, for which only very limited in vitro rationale and/or human data exist, before the agents are tested in adequately controlled trials in infected patients. While we understand that persons with serious and life-threatening conditions are willing to take significant and unknown risks associated with the use of new experimental drugs in the hopes that the drugs will offer even the slimmest chance of benefit, experience has shown that the widespread availability of new agents before they have undergone adequate clinical testing frequently slows, and in some cases, precludes the completion of trials to demonstrate their toxicity and efficacy. Unless access to these drugs is restricted until early controlled trials are completed, it is likely that the toxicity and efficacy of many potentially promising drugs will never be evaluated and, therefore, fewer drugs that are of real benefit will be developed and approved for marketing than

would otherwise be the case. If widespread availability of untested drugs is permitted, relatively safe but ineffective drugs will predominate and relatively toxic but effective drugs, such as AZT may not be approved. Such a situation would be a tragedy not only for AIDS patients today, but for HIV-infected patients in the future. Of course, while we are focusing on the need to collect data to help patients in the future, we are also mindful of the intense needs of patients facing death from AIDS. Medicine frequently is faced with the dilemma of balancing the needs of individual patients with the need to develop therapies for others.

As I mentioned above, effective treatment is the key. While we do not want to deprive people of hope, we also do not want to generate, or perpetuate, the false hope of a worthless product. The precise criteria for efficacy which must be met to allow approval of a treatment IND cannot be specified in advance and it is clear that the evidence or data demonstrating efficacy do not have to be as extensive, or as certain, as is necessary to support marketing approval of a new drug. However, a certain amount of evidence to demonstrate efficacy is crucial. Only then can we justify treatment use. As shown in the attached chart, we have allowed treatment INDs to proceed based on clinical experience usually found at the end of Phase II clinical trials in the mormal drug development process, before the hundreds or thousands of patients are studied in Phase III.

We are also making an effort to increase understanding of the process and develop industry consciousness of the advantages of treatment INDs. In this regard, we are soliciting applications from sponsors and are publishing each approval in both lay and medical publications. This

appears to be beginning to take hold as just this past month, we approved two treatment IND's sponsored by the industry.

I want you to know that I am personally committed to this process. I believe that it can, and will, be a viable approach to bringing important therapeutic products to the American public. Because I feel so strongly, I have participated actively in talking with the pharmaceutical industry and others to encourage them to pursue treatment INDs. In addition, I have published three artiticles in the scientific literature, co-convened a national conference with the American Medical Association on these new regulations and given numerous speeches about the treatment IND process.

Orphan Drugs

Some promising treatments relevant to AIDS have gained orphan drug status, making the manufacturer eligible for tax incentives and other benefits. Perhaps the best example of FDA's helping hand in the drug development process is pentamidine, a drug which is effective against Pneumocystis carinii pneumonia. Scientists at the CDC, FDA, and the company worked closely to ensure the availability of this life-saving drug to patients in the United States before the drug was approved in October 1984. In fact FDA and CDC conducted some of the laboratory and clinical work necessary to get the drug approved.

As of July 1, 1988, nineteen drugs for the treatment of AIDS and other AIDS-related conditions have received "orphan" designation. Eight of

these compounds are for the treatment of AIDS, three for Kaposi's sarcoma, five for Pneumocystis carinii pneumonia, and four for other opportunistic infections. Four grants for research on orphan drugs to treat AIDS have also been made.

Vaccines

Efforts are also being concentrated on developing an effective vaccine for AIDS. An important first step in the development of a vaccine to prevent infection by the AIDS virus occurred when, last August, FDA granted permission for the first clinical study in humans of an experimental AIDS vaccine. The vaccine, manufactured by MicroGeneSys, Inc. of West Haven, Connecticut, consists of purified HIV proteins developed using recombinant DNA techniques similar to those employed in the manufacture of other recombinant vaccines.

We approved a clinical trial for a second AIDS vaccine in November 1987. This vaccine, produced by Bristol-Myers Co. of New York City, is made from vaccinia virus into which genes coding for the AIDS virus surface proteins have been inserted by recombinant DNA techniques.

Most recently, we have granted an IND to the NIH for a study using the MicroGeneSys vaccine. We will also continue our efforts to help design studies in appropriate animal models and clinical trial protocols to foster the development of a vaccine.

Research

In addition, FDA staff are actively involved in AIDS research in several areas, applied or relevant to new regulatory mission. We also coordinate our activities frequently with our colleagues at NIH, who have the lead responsibility for AIDS research. It should be emphasized that the focus of our research is generally much different from that of NIH-conducted research. At FDA we focus on research that will facilitate our regulatory actions. Among our research projects are comparative analyses of diagnostic tests, the development of methods to validate vaccine safety, studies of the basic immunologic defects associated with AIDS, examinations of the biological and chemical properties of natural interferons and their ability to modify the immune system, and efforts to develop in primates an animal model for AIDS research. We are also funding extramural AIDS-related research, including research on testing for HIV antibodies in blood donors. Finally, our Center for Drug Evaluation and Research (CDER) has initiated a major new research effort focusing on optimizing dosages of AIDS drugs as they are developed. The first candidate AIDS drug being investigated in this new research effort is dextran sulfate which I mentioned earlier. Our Centers for Food Safety and Applied Nutrition, Devices and Radiological Health, and Veterinary Medicine are also involved in research related to AIDS.

Fraudulent Products

We have recently seen an increase in the number of fraudulent products intended for AIDS patients and those who fear coming down with the disease. So-called "treatments" include blue-green algae, injections of hydrogen peroxide, the food preservative BHT, pills derived from mice that have been given the AIDS virus, and herbal capsules that contain poisonous metals. For uninfected consumers, there are also products such as the "Sani-Form," a piece of plastic to cover telephone mouthpieces that was promoted to protect against infection from public phones. This type of product, of course, not only takes people's money, but erroneously promotes the idea that AIDS can be contracted by touching items handled by someone infected with HIV.

To counter these forms of fraud, we have mobilized our field inspectional force to investigate those promoting fraudulent claims.

Education and Information

The FDA has taken an active role in the efforts of the Department of Health and Human Services toward educating both the public and the medical community about AIDS.

Specifically, we have issued special publications of our FDA Drug Bulletin, which were mailed to over a million physicians and other health care professionals, and developed an award winning information package for the medical community which is exhibited and distributed at

health professional meetings. In addition, an article, "AIDS Education," appeared in the September 1987 issue of the FDA Consumer magazine which is sent to approximately 22,000 subscribers. We also issue a monthly update on AIDS drugs that are under development and review. On April 15, 1988, we published an article in the Journal of the American Medical Association describing FDA's new treatment IND process. I will submit these for the record.

In the area of health fraud, we have prepared numerous articles for health care publications such as the FDA Consumer, Journal of the American Medical Association, and American Academy of Family Physicians Reporter and initiated a public information program to alert AIDS patients and consumers to fraudulent products. In addition, a National Health Fraud Conference, cosponsored by FDA, was held March 13-15, 1988, in Kansas City. At the conference, a plenary session was devoted entirely to AIDS fraud. Close working relationships have been established with the California Attorney General's Task Force on AIDS Fraud and the City of New York's Department of Consumer Affairs. Information on AIDS fraud has also been shared with the Federal Trade Commission, United States Postal Service, Environmental Protection Agency, and State and local food and drug officials.

We also have begun the process of establishing a comprehensive approach to improve communication with the AIDS community. In this regard, we have met with key New York City and State officials and their staffs and others who service and liaison with AIDS constituencies to help us identify and communicate with the most appropriate leaders of the AIDS

community. We also plan to meet with the AIDS liaison staffs of other city and State agencies in order to expand this important initiative.

Finally, the FDA is engaged also in developing informational materials on surgical gloves and on the proper handling and disinfection of other medical devices such as dental drills, endoscopes, hospital equipment, etc. We are also preparing an educational brochure on condoms.

THE FUTURE

The task ahead for public and private organizations trying to develop AIDS therapies is enormous. Fortunately, the extensive research on AIDS drugs that has been underway since the early 1980's has begun to yield results. As the attached graphs demonstrate, NIH research continues to grow in response to the AIDS epidemic. There are also increases in the research budgets of other Public Health Service agencies. The combination of Federal efforts with those in the private sector should result in a continuation of the rapid growth that we are already seeing in the number of INDs for AIDS therapies. We anticipate that greater than 60 percent of the applications for therapies for AIDS will come from the private sector. For example, of the nineteen AIDS products which have received orphan designation, seventeeen are from the private sector. We must be prepared to evaluate studies rapidly to determine the safety and effectiveness of these therapies.

As research increases, FDA's ability to review the potential new products that everyone expects to flow from this research must increase

concurrently. We must never become a bottleneck in the successful development of AIDS treatments. This capability must include guidance to drug developers in designing research protocols as well as timely premarket review. Indeed, I believe FDA should be a bridge between the scientists who do the research and the patients who need the products of that research.

Fortunately, we at FDA have some experience with building bridges. And over the years we have evolved five key elements for assuring the expeditious transfer of new drugs to patients.

The first is the all-important initial communication with the sponsor. FDA staff, sometimes including myself, meet with new drug and vaccine sponsors to help them design their clinical trials.

Second, we continue that communication during Phase II and Phase III testing, to protect against false starts and to assure that our expertise in designing clinical trials is provided to sponsors. We work particularly closely with our colleagues at NIH, and also with many small companies that traditionally have not been involved in drug development of this sort.

Third, we must always remember the crucial element of public confidence. Americans must know that the drugs and vaccines they use have been given the rigorous "stamp of approval" of FDA scientists--that they can be confident that their therapies are safe and effective.

Fourth, we have developed a way of getting a good product over that bridge before the span is fully completed. I am referring to the treatment IND regulation I mentioned earlier. With treatment INDs, we can permit the use of promising experimental drugs for desperately ill patients while clinical trials are being completed--as we did with AZT and are now doing with trimetrexate.

Finally, FDA must have enough workers to build that bridge. As public and private AIDS research increases, demands will flow to FDA from drug developers for guidance in designing research protocols and for final product review. When that happens--as it is already beginning to--FDA must be a catalyst and facilitator, not a rate-limiting factor slowing the movement of products across my theoretical bridge.

Clearly, FDA is a personnel-intensive organization. That is, we need people to get the job done. However, it is difficult, if not impossible, to predict what our precise needs will be in order to be prepared for the inevitable increase in our workload. Therefore, we will continue to assess our evolving needs and to discuss those needs with Department officials to secure the necessary resources to prepare ourselves for the expected future demands for all of our AIDS-related activities. As noted earlier, the President's FY 1989 budget already includes significant FDA personnel increases for AIDS Activities. We are also working closely with the Institute of Medicine and the Pharmaceutical Manufacturers Association to develop creative new solutions to our manpower recruitment and retention problems--solutions

such as fellowship programs, improved automation, and assistance from academia.

CONCLUSION

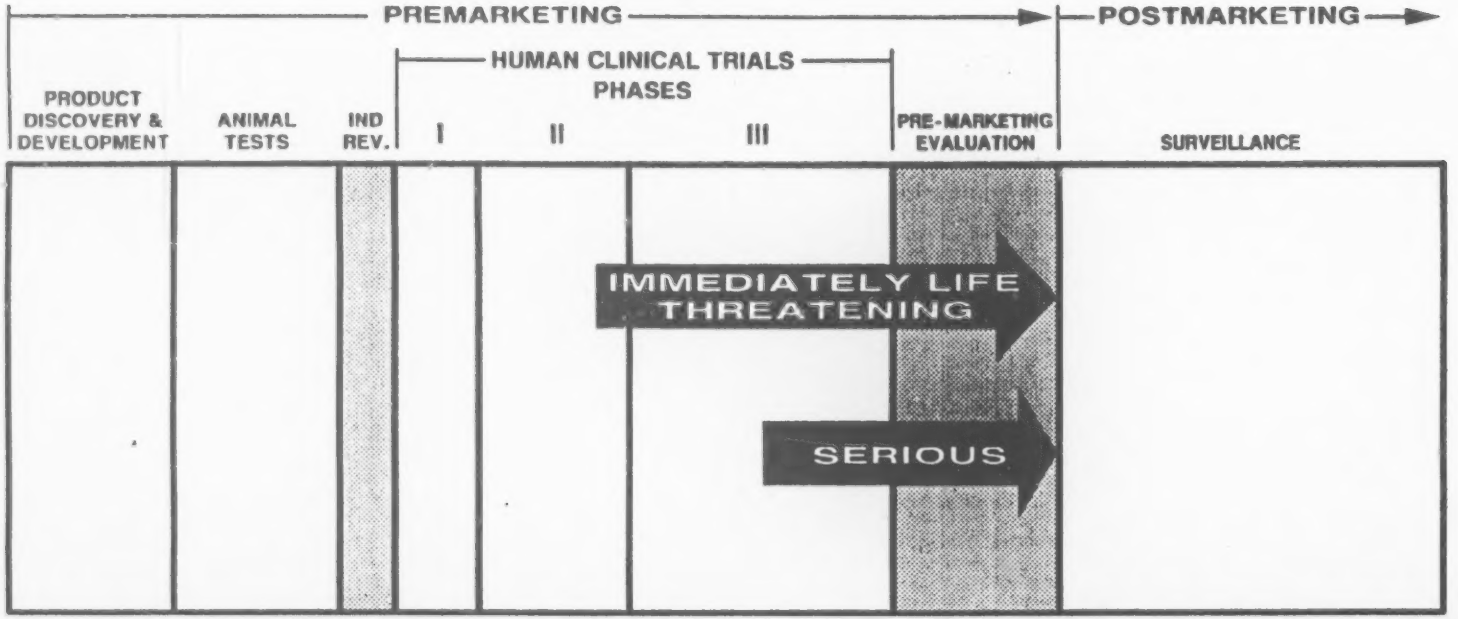
Let me conclude by saying that we fully understand the concern over the amount of time needed for clinical testing, as opposed to the desire--which we all share--to provide effective treatment immediately to people with AIDS. FDA's policy for research and review of potential AIDS drugs is to maintain an approach that is flexible and compassionate, but carefully balanced between these concerns and the possibility of worsening, rather than helping, the condition of AIDS patients as a result of premature distribution of an experimental drug. We do not believe it would be to the advantage of these patients to widen the scope of drug distribution too rapidly--before important information on the drug's effects becomes available. Each decision will be reached on the the evidence available. There are no hard and fast ground rules thereby giving the Agency flexibility in reaching decisions. The experience with earlier drugs has shown the difficulties that can be encountered. Early experience suggested that certain drugs might be useful, but significant toxicity, capable of worsening the patient's already bad situation, limited their potential.

We are engaged in a war on AIDS. We must, and we will, continue our efforts to find effective therapies to treat, cure, and prevent this dreaded disease, and we will do so with compassion both for the people

with AIDS who suffer and die and for their families and friends who love and care for them.

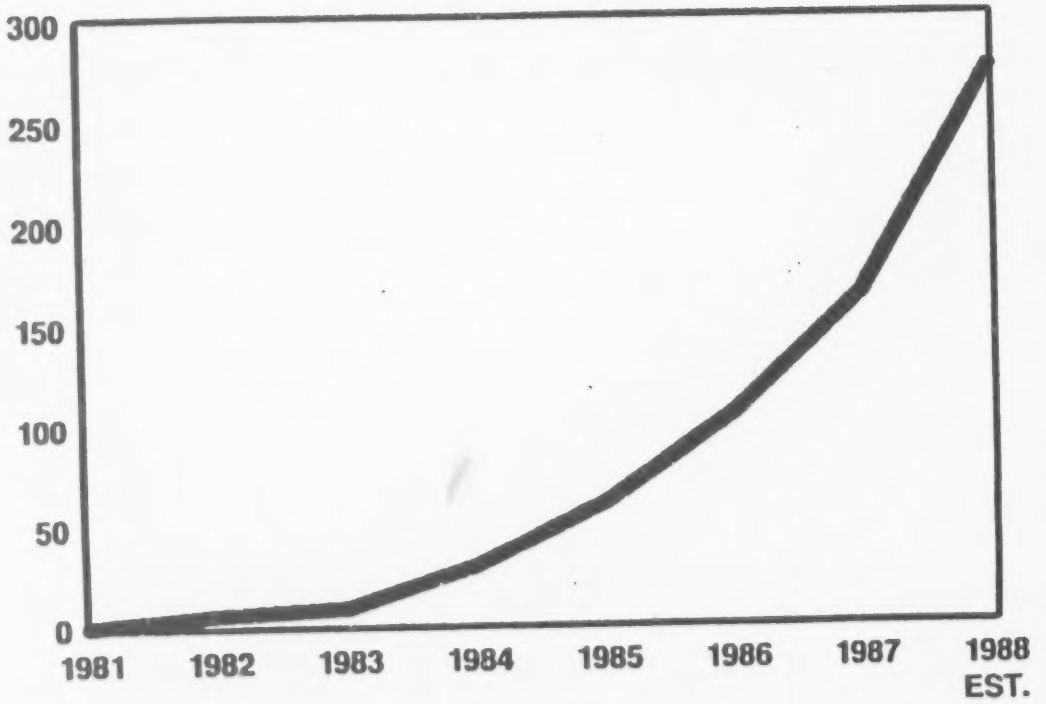
This concludes my formal statement. If you have any questions, my colleagues and I will be happy to answer them.

DRUG DEVELOPMENT PROCESS: TREATMENT USE



89-340 O - 88 -- 4

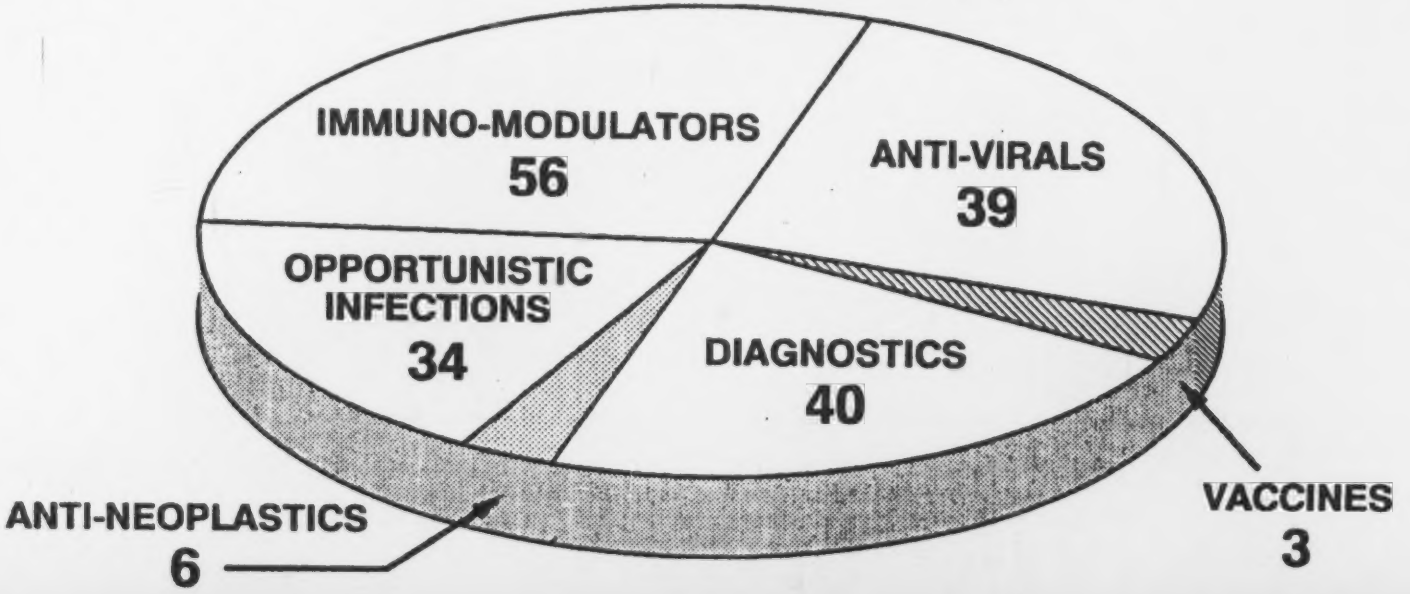
AIDS INDs



AIDS INDs

TOTAL = 178

Active as of June 1, 1988



PROJECTION METHOD

- INCLUDES ALL THERAPIES FOR AIDS SUCH AS ANTIVIRALS, OPPORTUNISTIC INFECTIONS, IMMUNOMODULATORS AND ANTINEOPLASTICS. EXCLUDES VACCINES AND DIAGNOSTICS.
- CONVERTS THE TOTAL NUMBER OF AIDS INDs INTO DISTINCT THERAPIES (CURRENTLY 63), AND ASSUMES THAT 14 ADDITIONAL THERAPIES PER YEAR (1987's RATE) CONTINUES UNTIL THE YEAR 2000.
- ASSUMES THAT AIDS THERAPIES ARE TWICE AS DIFFICULT TO BRING TO THE POINT OF A MARKETING APPLICATION AS CONVENTIONAL DRUG THERAPIES.
- ASSUMES FDA APPROVAL RATE IDENTICAL TO HISTORIC RATE FOR MORE DIFFICULT CONVENTIONAL DRUG CATEGORIES, E.G. ONCOLOGICAL PRODUCTS.
- MODELS A TOTAL DEVELOPMENT TIME (IND START TO NDA APPROVAL) FOR AIDS THERAPIES WHICH IS TWICE AS FAST AS THAT FOR CONVENTIONAL DRUG THERAPIES.

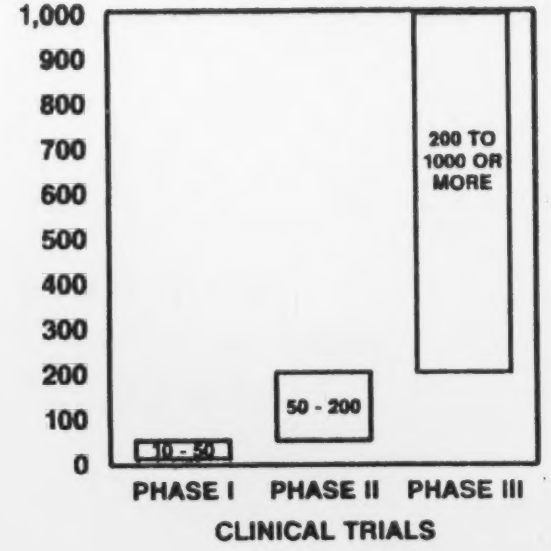
STATISTICAL PROJECTION OF THE SUCCESSFUL THERAPIES FOR AIDS AND ITS COMPLICATIONS

YEAR	CUMULATIVE NUMBER OF:			
	AIDS INDs	DISTINCT THERAPIES UNDER STUDY	MARKETING APPLICATIONS FOR DISTINCT THERAPIES	ADDITIONAL SUCCESSFUL THERAPIES*
1991	320	99	6	1-2
1995	520	155	14	5-6
2000	720	215	24	9-11

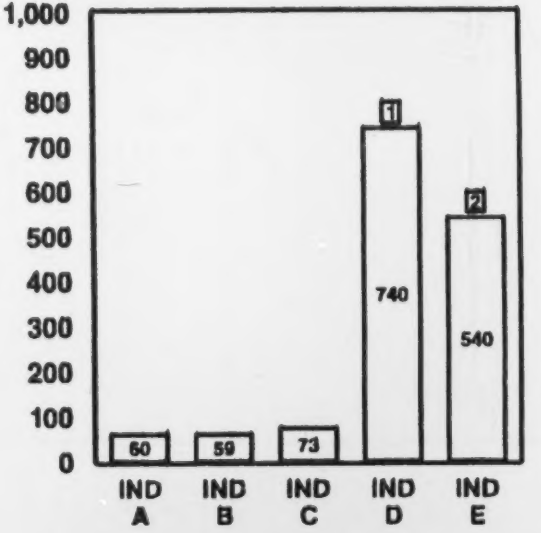
* IN ADDITION TO ZIDOVUDINE (AZT)

NUMBER OF PATIENTS STUDIED PRIOR TO APPROVAL OF NDAs VS. TREATMENT INDs

AVERAGE FOR APPROVED NDAs



5 APPROVED TREATMENT INDs

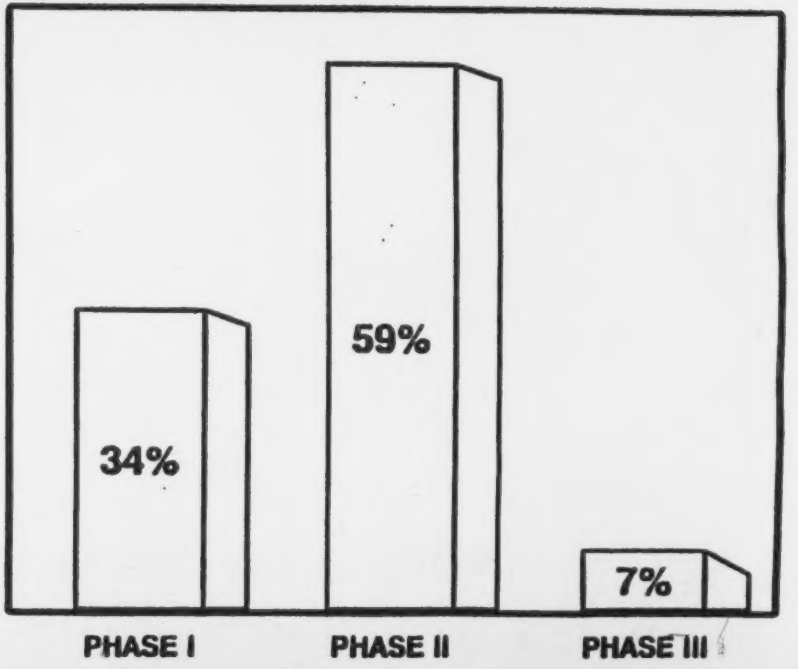


1. UNDER INVESTIGATIONAL USE FOR MORE THAN 15 YEARS (IS CURRENTLY MARKETED IN FOREIGN COUNTRIES).
2. PRODUCT DEVELOPMENT AND SUBMITTED AS AN NDA.

NOTE: MOST TREATMENT INDs REFLECT COLLECTIVE PATIENT EXPERIENCE, USUALLY FOUND AT THE END OF PHASE II CLINICAL TRIALS IN NDA DEVELOPMENT

APPROVED AIDS INDs
BY TESTING PHASE

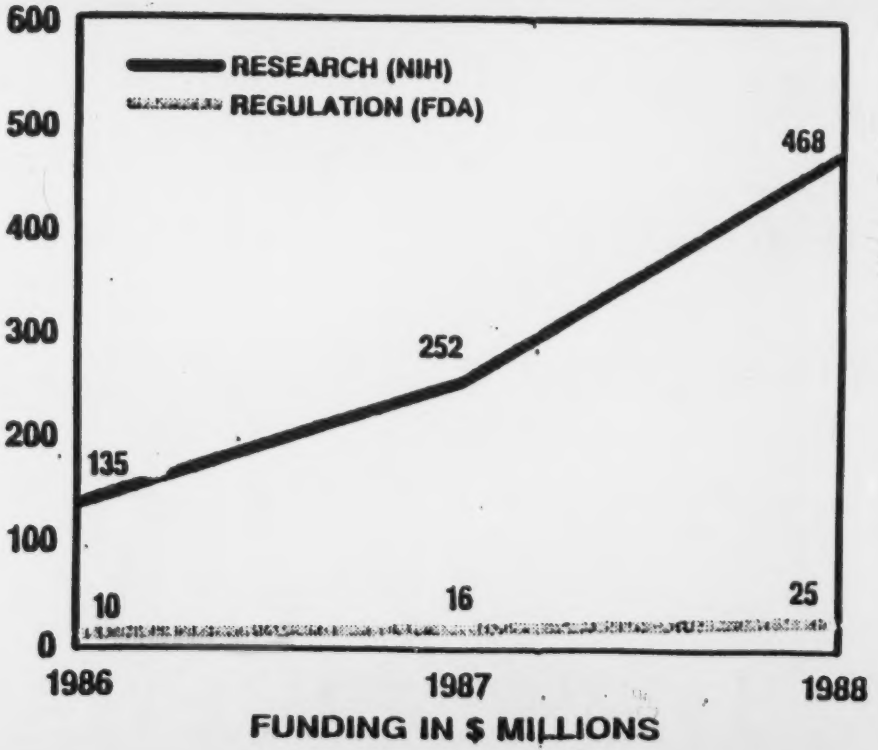
DRUG AND VACCINE
APPROVED INDs
AS OF 6/1/88



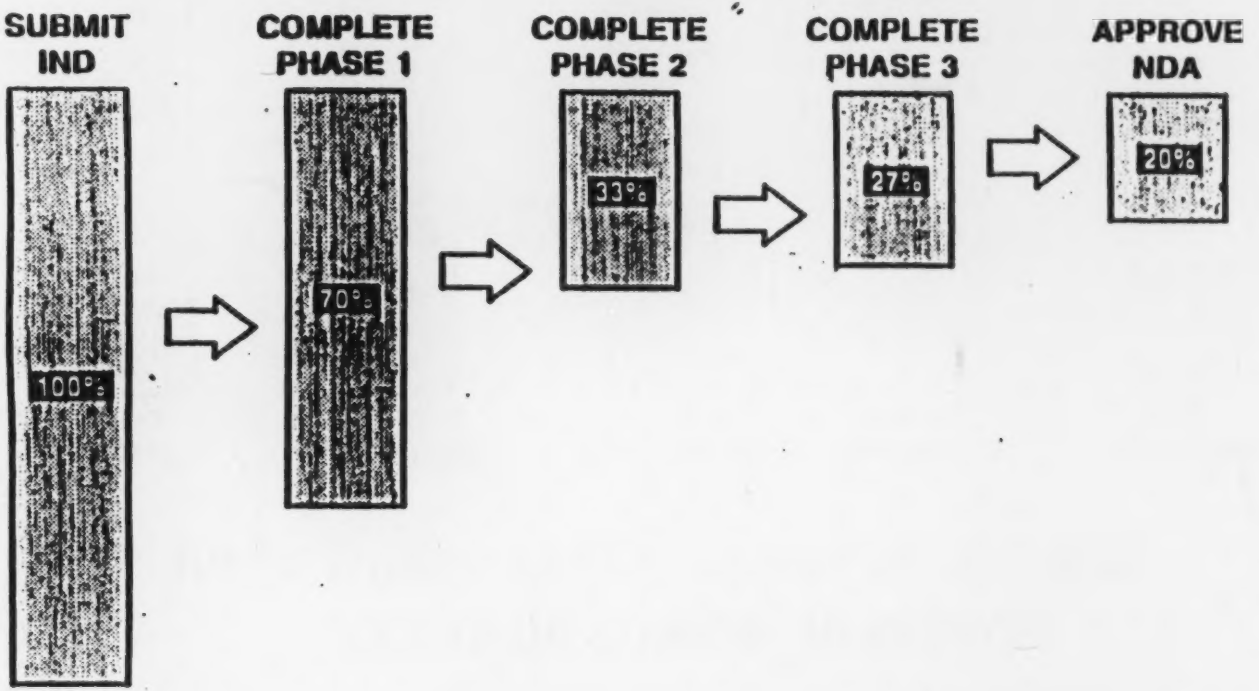
APPROVED TREATMENT INDs

KIDNEY TRANSPLANTS	OCTOBER 1987
GERM CELL CANCER	DECEMBER 1987
AIDS INFECTION (PCP)	FEBRUARY 1988
OBSESSIVE - COMPULSIVE DISORDER	JUNE 1988
PARKINSON'S DISEASE	JUNE 1988

AIDS RESEARCH AND REGULATORY FUNDING



SUCCESS OF CLINICAL RESEARCH
(NCEs SUBMITTING FIRST INDs IN 1976-1978)



SUCCESS OF CLINICAL RESEARCH
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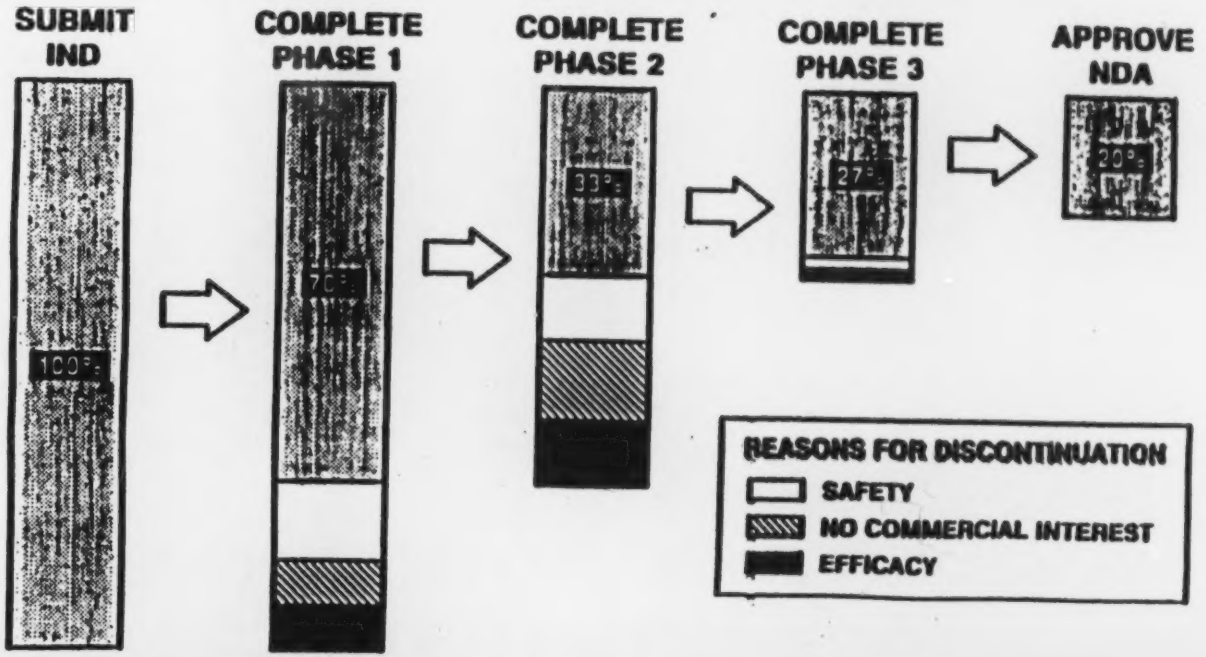

Submission for the Record

(Dr. Young's Formal Statement
Page 22, Line 7)

Hearing Before The

Committee on Labor and Human Resources
United States Senate

July 13, 1988

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FDA Drug Bulletin

October 1985 Volume 15 Number 3

Messages from Secretary Heckler And Commissioner Young

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PHS Recommendations For Screening Blood

Recommendations For Patients With Reactive Tests

Precautions For Health Care Practitioners

Case Definition

Epidemiology

Prevention and Treatment

FDA Drug Bulletin

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Other Health Professionals

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FDA Drug Bulletin
Circulation Dept., HFI-43
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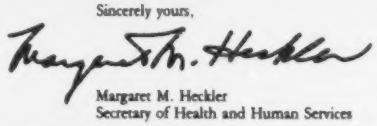
Rockville, MD 20857

Message from Secretary Heckler

Over the past two years, scientists at the National Institutes of Health and others in France have identified the virus that causes AIDS and have developed an antibody-screening test for donated blood. Surveillance by the Centers for Disease Control continues to assess the extent of this growing public health problem and enables the Public Health Service to issue recommendations to health professionals to prevent the spread of this deadly disease. In addition, FDA is encouraging research on drugs and biologics to fight both the virus and the opportunistic infections associated with AIDS.

We have accomplished much in a short time. Yet AIDS continues to spread and the urgency of our educating both health professionals and the general public about this disease increases, as does the necessity of funding research to develop medical treatments and a vaccine for AIDS. I pledge that this effort will continue to be HHS's number one priority.

Sincerely yours,



Margaret M. Heckler
Secretary of Health and Human Services

Letter from Commissioner Young

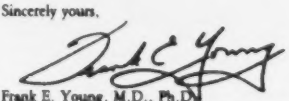
Dear Colleague:

I join Secretary Heckler in recognizing the urgency of finding ways to contain the spread of AIDS and to make available treatments for those stricken.

As with the speedy licensing of test kits for screening blood for antibodies to HTLV-III, FDA is giving highest priority to AIDS-related drugs and biologics. We are providing research incentives through our Orphan Products Development Program and are working closely with manufacturers submitting plans for clinical studies. We also make certain drugs available for "compassionate" or "treatment" use while they are under study.

This special issue of the *FDA Drug Bulletin* summarizes current knowledge about HTLV-III and efforts to prevent its spreading. It augments my previous "Dear Doctor" letter of March 8, 1985. Our publications will continue to keep health professionals informed of progress on AIDS.

Sincerely yours,



Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

Progress On AIDS

The identification of the virus responsible for acquired immunodeficiency syndrome (AIDS) has made possible an effective blood antibody screening test and the updating of the AIDS case definition. This causative virus has been named human T-lymphotropic virus type III (HTLV-III) by researchers at the National Institutes of Health (NIH) and lymphadenopathy-associated virus (LAV) by French researchers at the Pasteur Institute.

An intensive research effort is under way to find drugs and therapeutic biologics and a vaccine that could be used to treat or prevent the development of this generally fatal disease.

Blood Supply Safer

Use of screening tests for HTLV-III antibody on donated blood and plasma is successfully preventing the virus responsible for AIDS from entering the blood supply.

Conferees at a July 31, 1985, workshop Bethesda, Md., cosponsored by the National Institutes of Health (NIH), FDA and the Centers for Disease Control (CDC), heard that blood and plasma collecting facilities have begun routine testing for this antibody and that all blood found to be reactive must be discarded. At the workshop, representatives from the American National Red Cross, the American Association of Blood Banks, the Council of Community Blood Centers, the Greater New York Blood Program and the American Blood Resources Association agreed that the tests are effective in protecting the public from receiving blood containing HTLV-III.

FDA reported data from a survey of more than 1.1 million units of blood collected and tested for HTLV-III antibody by 155 centers of the major blood organizations through June 16, 1985.[1] Of this total, 2831 units (0.25%), or about 1 in 400, were reported to be repeatedly reactive for antibody using the licensed enzyme-linked immunosorbent assays (ELISA or EIA) originally developed by NIH scientists.

The pattern of positive tests varied slightly in different regions of the country and according to the manufacturer's test kit used. This frequency of repeatedly reactive donors was consistent with the data obtained in clinical trials conducted prior to the licensure of the three manufacturers' reagents.

CDC and the Atlanta Region of the American Red Cross reported data from testing more than 51,000 blood donors of whom 0.23% were repeatedly reactive.[2] Of 106 repeatedly reactive units, 34 (32%) were strongly reactive and these correlated highly with both positive Western blot tests (94%) and positive culture for HTLV-III (56%). By contrast, in 220 donors whose tests were initially reactive but subsequently negative, as well as in a random sample of 50 donors with completely negative tests, none had a positive Western blot and none had a positive virus culture.

While donors with repeatedly reactive tests are equally distributed between males and females, those with strongly reactive tests that correlated closely with positive Western blot and virus culture results were more apt to be male.

Of repeatedly reactive donors interviewed, 89% of those with strongly reactive tests were found to have identifiable risk factors for HTLV-III infection, while none of those with weakly reactive tests had risk factors. Thus, of the approximately 3 in 1200 blood donors found to be repeatedly reactive, about 1 in 1200 will likely be infected with HTLV-III, while about 2 in 1200 will probably be representative of nonspecificity in the test rather than infection.

The reason for this nonspecificity is unknown but probably represents, at least in part, the effect of antibody directed against the human cells used to grow the virus in producing test reagents.

To measure test sensitivity, antibody tests and virus isolation attempts were made on blood samples from high-risk persons attending a clinic for sexually transmitted diseases in San Francisco. None of 70 men with negative HTLV-III antibody tests had a positive virus culture; 43 (60%) of 72 with repeatedly reactive tests were culture-positive. Among these 72 antibody-positive blood samples, 70 (97%) were highly reactive and 97% of those tested to date had a positive Western blot test as well.

Plasmapheresis facilities are generally notifying donors when a repeatedly reactive EIA test result is obtained. Blood banks at present are often seeking confirmation of EIA reactive results by Western blot before notifying donors.

Fewer than 2% of reported AIDS cases have been thought to be transmitted by blood transfusion. Even this risk will be virtually eliminated with the application of the new test coupled with the continued use of self-exclusion criteria for high risk donors.

In September 1985, these criteria were broadened to include not only members of high-risk groups,[3] but also any man who has had sex with another man since 1977, including those who had only a single homosexual experience. This change was prompted by the discovery that the majority of individuals having confirmed positive HTLV-III test results have been homosexual or bisexual males who felt they were not in a risk group.[4]

Because the incubation period for AIDS can be more than five years, new cases of transfusion-associated AIDS can be expected to appear for some time in persons infected with HTLV-III before the blood screening test came into use.

In addition to its use in screening donated blood, Public Health Service (PHS) has recommended that the EIA for HTLV-III antibody be used to screen blood and serum from donors of organs, tissue or semen intended for human use, and that the test result be used to evaluate the appropriate use of such materials from these donors.[5]

Data have established that hemophilia A patients treated with Factor VIII concentrates had a significantly greater risk of contracting AIDS than any other blood (or blood product) recipient group.[6] Recent adoption of heat (or chemical) processes to inactivate viruses, including HTLV-III, by U.S. licensed manufacturers of Factor VIII, together with the screening of the blood supply, have now virtually eliminated this risk. Factor IX concentrate, used to treat hemophilia B, has only rarely been thought to transmit HTLV-III; however,

a viral inactivation step is being added to its manufacturing process as well.

FDA Letter

In a letter mailed to physicians in March 1985, preceding the approval of the first EIA test kit, FDA emphasized that the screening kits do not constitute a diagnostic test for AIDS, but rather are useful to identify—through the presence of antibody—those who have been infected by HTLV-III and therefore might transmit the disease. As with any serologic test, there will be some false-positive results even in repeatedly reactive samples. These apparently aberrant results may represent biologically false-positive reactions such as cross reactivity to other antigens or nonspecific reactions. Positive antibody test results are more likely to be a true indication of HTLV-III infection when the prevalence of infection by the virus in the population being screened is higher.

PHS Recommendations

PHS has issued recommendations for screening donated blood for HTLV-III antibody.[7] Summarized, these include:

- Screening all plasma and blood for HTLV-III antibodies.
- Blood or plasma that is reactive for HTLV-III antibody should not be transfused or used for manufacture into injectable products capable of transmitting infectious agents.
- Notifying the donor only upon a positive result from a second EIA or other test (e.g., Western blot) and referring the donor to a physician for evaluation.
- Keeping positive test results confidential. Whenever possible, donor deferral lists should be general, without specifying the reason for inclusion on the list.

Recommendations For Patients With Reactive Tests

Physicians and other health practitioners whom patients consult after having been told they have repeatedly reactive test results can advise their patients of the following: [7]

- The prognosis for an individual infected with HTLV-III over the long term is not known. However, data suggest that most persons will remain infected for life.
- Even though asymptomatic, persons with repeatedly reactive HTLV-III antibody tests may transmit infection to others through sexual intercourse, sharing of needles and, possibly, exposure of others to saliva through oral-genital contact or intimate kissing. Recent research has revealed that HTLV-III is also present in the tears of AIDS patients but there is no evidence of transmission through tears. The efficacy of condoms in preventing infection with HTLV-III is unproven, but the consistent use of them may reduce transmission. Toothbrushes, razors, or other implements that could become contaminated with blood should not be shared.
- Regular medical evaluation and follow up is advised, especially for patients who develop signs and symptoms suggestive of AIDS.
- Persons with repeatedly reactive HTLV-III antibody tests should not donate blood, plasma, body organs, other tissue or sperm.
- Women with repeatedly reactive antibody tests or whose partners are seropositive, are at increased risk of acquiring AIDS. If they become pregnant their offspring are also at increased risk.
- If persons with repeatedly reactive antibody tests have accidents involving bleeding, contaminated surfaces should be cleaned with household bleach freshly diluted 1:10 in water.
- When seeking medical, dental or eye care, these persons should advise the practitioner of their positive antibody status so that appropriate evaluation can be undertaken and precautions can be taken to prevent transmission to others.
- Devices used on these patients that have punctured the skin (such as hypodermic and acupuncture needles) should be steam-sterilized by autoclave before reuse or safely discarded. Whenever possible, disposable needles and equipment should be used.
- Testing for HTLV-III antibody should be offered to persons who may have had intimate contact with seropositive individuals (e.g., sexual partners, persons with whom needles have been shared, infants born to seropositive mothers).

Patients and their families can also be advised there is no evidence that HTLV-III is transmissible by casual contact including: living in the same house as an infected person; caring for an AIDS patient; eating food handled by an infected person; being coughed or sneezed upon by an infected person; casual kissing; or swimming in a pool with an infected person.

As with most other infectious diseases, the spectrum of responses to HTLV-III infection is varied. Because it represents the end of the spectrum, AIDS is the most easily recognized of these responses. But as with other viruses (e.g., poliomyelitis), infection with HTLV-III probably does not inevitably result in the worst outcome. Preliminary estimates by CDC suggest that fewer than approximately 10% of those infected have thus far developed AIDS; approximately 25% have had only relatively minor problems such as chronic lymphadenopathy. About two-thirds of infected persons have remained asymptomatic, at least in the short term.

Precautions For Health Care Practitioners

PHS previously recommended procedures for lab personnel,[8] dentists and morticians[9] having contact with AIDS patients.

Recently, after NIH scientists isolated HTLV-III virus in tears, NIH, CDC and FDA issued recommendations in the *Morbidity and Mortality Weekly Report* of Aug. 30, 1985 (34:533-534). Summarized, they are:

- Health care professionals performing eye examinations or other procedures involving contact with tears should wash their hands immediately after a procedure and between patients. When practical and convenient, disposable gloves should be worn. The use of gloves is advisable when there are cuts, scratches or dermatologic lesions on the practitioner's hands.
- Instruments that come into direct contact with external eye surfaces should be wiped clean and then disinfected by:

a) a 5- to 10-minute exposure to a fresh solution of 3% hydrogen peroxide, or

b) a fresh solution containing 5,000 parts per million (mg/L) free available chlorine—a 1/10 dilution of common household bleach (sodium hypochlorite), or

c) 70% ethanol, or

d) 70% isopropanol.

The device should be thoroughly rinsed in tap water and dried before reuse.

- Contact lenses used in trial fittings should be disinfected between each fitting. Hard lenses, rigid gas permeable lenses, and soft lenses should be disinfected with a commercially available hydrogen peroxide contact lens disinfection system currently approved for soft contact lenses. Alternatively, some hard lenses and soft lenses can be disinfected by heat disinfection. Rigid gas permeable lenses may warp if heat-disinfected.

Case Definition

As originally defined,[10] the clinical definition of AIDS follows four major patterns:

(1) A febrile prodrome of weeks to months followed by opportunistic infection

(2) Abrupt onset of opportunistic infection

(3) Presentation with Kaposi's sarcoma

(4) Progression from AIDS-related complex.

As a result of the identification of HTLV-III and the development of reliable blood screening tests, this case definition was revised by CDC in June 1985 in response to recommendations by the Conference of State and Territorial Epidemiologists (CSTE)[11] and now includes the following refinements:

- In the absence of the opportunistic diseases required by the current case definition, any of the following diseases is considered indicative of AIDS if the patient has a positive serologic or virologic test for HTLV-III:
  - —disseminated histoplasmosis (not confined to lungs or lymph nodes) diagnosed by culture, histology or antigen detection
  - —isosporiasis, causing chronic diarrhea (more than 1 month), diagnosed by histology or stool microscopy
  - —bronchial or pulmonary candidiasis, diagnosed by microscopy or by presence of characteristic white plaques grossly on the bronchial mucosa (not by culture alone)
  - —non-Hodgkin's lymphoma of high-grade pathologic type (diffuse, undifferentiated) and of B-cell or unknown immunologic phenotype, diagnosed by biopsy
  - —histologically confirmed Kaposi's sarcoma in patients who are 60 years old or older when diagnosed.
- In the absence of the opportunistic diseases required by the current case definition, a histologically confirmed diagnosis of chronic lymphoid interstitial pneumonitis in a child (under 13 years of age) is considered indicative of AIDS unless test(s) for HTLV-III are negative.
- Patients who have a lymphoreticular malignancy diagnosed more than 3 months after the diagnosis of an opportunistic disease used as a marker for AIDS will now be included as AIDS cases.
- To increase the specificity of the case definition, patients are excluded as AIDS cases if they have a negative result on testing for serum antibody to HTLV-III, have no other type of HTLV-III test with a positive result, and do not have a low number of T-helper lymphocytes or a low ratio of T-helper to T-suppressor lymphocytes. In the absence of test results, patients satisfying all other criteria in the definition continue to be included.

In accordance with these recommendations, only AIDS—the more severe manifestation of HTLV-III infection—will be reportable nationally. The reportability of milder disease associated with HTLV-III infection (AIDS-related complex [ARC] and persistent generalized lymphadenopathy [PGL]), as well as asymptomatic infections will continue to be determined by individual states.

ARC is a clinical and laboratory syndrome characterized by minor conditions clinically associated with immunosuppression (e.g., oral thrush) and laboratory evidence of immunosuppression probably associated with HTLV-III infection. In addition, unexplained idiopathic thrombocytopenia is probably associated with HTLV-III infection, as are a variety of non-life-threatening fungal, viral and bacterial infectious processes that probably represent manifestations of virus-induced immunologic perturbation. These manifestations are sometimes termed lesser AIDS.

PGL is also recognized as being associated with HTLV-III infection. It is a symptom complex characterized by the occurrence of persistent, unexplained lymph node enlargement in several extra-inguinal lymph node groups. The relationship of the lymphadenopathy syndrome to progression to overt clinical AIDS is uncertain but probably is as high as 10%. (Of course, physicians are aware that PGL can be caused by agents other than HTLV-III.)

Approaches to clinical evaluation of AIDS and its diverse related clinical disorders were discussed in PHS informational material mailed by FDA to physicians on March 8, 1985. Health professionals who did not receive this information may obtain it from: FDA (HFI-40), 5600 Fishers Lane, Rockville, MD 20857.

Epidemiology

CDC reports the following epidemiological description of AIDS cases:

Between June 1981 and Sept. 16, 1985, 13,228 persons in the United States were reported to have been diagnosed as having AIDS. Of these, 6758 (including 116 children) are known to have died. Of the total number of cases, 57% had *Pneumocystis carinii* pneumonia (PCP) without Kaposi's sarcoma (KS); 19% had KS without PCP; 18% had opportunistic infections without KS or PCP; and 6% had both KS and PCP. Seventy-three percent of the adult/adolescent cases occurred in homosexual or bisexual males; 17% in intravenous drug abusers; 1% (92 cases) in patients with hemophilia or other coagulation disorders; 1% (133

cases) through heterosexual contact with a person who had AIDS or who was at high risk (of these, 118 cases occurred in women and 15 in men); 2% (204 cases) through transfusion with blood or blood products; 6% (829) in none of these categories.

Seventy-one percent of the pediatric cases occurred in children whose parents had AIDS or were at increased risk for AIDS, with epidemiologic data suggesting transmission from infected mother to child before, at, or shortly after birth. Five percent occurred in children with hemophilia or other coagulation disorders; 16% in those who had received blood or blood products transfusion; and 8% in none of these categories.

The highest number and percentage of AIDS cases were reported in New York State (35%, 4669 cases). California followed with 23% (3067 cases). Florida reported 7% of the cases, New Jersey 6%, and Texas 5%. The following each reported 2% of the cases: Pennsylvania, Illinois, Massachusetts, Georgia and the District of Columbia. The following each reported 1% percent of the cases: Maryland, Puerto Rico, Washington, Connecticut, Louisiana, Virginia, Colorado, Ohio and Michigan. The following each reported 10 or more cases but less than 1% of the cases: North Carolina, Missouri, Arizona, Indiana, Iowa, Hawaii, Kansas, Oregon, Minnesota, Wisconsin, South Carolina, Alabama, Kentucky, Tennessee, Oklahoma, Rhode Island, Utah, Delaware, Nevada, Iowa, New Mexico, West Virginia and other states and territories. The only states reporting no cases were Montana, North Dakota and South Dakota.

The number of cases per million population is 58.1 for the entire United States but varies greatly in different metropolitan areas. In New York City, from June 1981 to Sept. 16, 1985, there were 471.9 cases per million population, and in San Francisco there were 461.8 cases per million population. The three other metropolitan areas with the highest cases per million were Miami, Fla., with 270, Newark, N.J., with 166.3, and Los Angeles with 150.5. In contrast, areas outside these metropolitan areas had 27.1 cases per million population.

Prevention and Treatment

Many agents have been used to combat the multitude of infections to which AIDS victims are susceptible. Although some of these treatments have been effective in temporarily halting these infections, the persistence of the underlying immune defect ensures that they will recur or be replaced by other equally serious infections.

The only hopes for curing AIDS are by attacking and destroying the HTLV-III virus or correcting the underlying immune defect. Because there is no specific therapy for AIDS at the present time, it is necessary to take certain prevention and education measures to reduce the threat of AIDS and create a better awareness of the disease. This has generally been accomplished as new information develops through communications from various PHS agencies.

As with many other viral diseases, the most effective way of preventing AIDS is through the use of a vaccine that would protect against HTLV-III infection. NIH scientists have initiated a major effort to develop a vaccine. This involves searching for antigenic components of the virus that would be capable of stimulating the production of virus-neutralizing antibodies. A number of novel approaches are being explored including several that involve application of the new recombinant DNA technology. Several of these experimental preparations have been inoculated into animals and any that appear promising will be scheduled for clinical trial in small numbers of volunteers.

A major effort is under way to find drugs that would be effective in treating AIDS patients and others already infected with the virus. The status of such research was discussed at a workshop cosponsored by NIH, FDA and CDC, held at NIH on June 3, 1985. Participants from around the world discussed studies conducted with antiviral agents that suppress the replication of HTLV-III and with other substances capable of stimulating the damaged immune system. Now that methods for propagating HTLV-III in the test tube are widely available, *in vitro* screening of drugs for antiviral activity can be quickly accomplished. Thus, many compounds in addition to those already under study will be identified as deserving of clinical evaluation.

Although to date no treatment has been proven to effectively combat HTLV-III infection, several agents are already under investigation. Those discussed at the workshop, at other professional meetings, in the literature and in the news media fall into two categories—antivirals and immune stimulators.

ANTIVIRALS

HTLV-III has an envelope that is heavily glycosylated. A retrovirus, HTLV-III uses its RNA to produce a DNA which in turn produces the RNA responsible for the viral proteins. The production of the DNA is dependent upon the viral enzyme, reverse transcriptase (RT). Theoretically, an effective agent would either effect a change in the viral envelope, alter the membrane of the target cell to prevent adsorption of the virus, or interfere with one of the steps in the viral replication, such as RT. The latter has been the presumed mechanism of action of most antiviral agents investigated to date. Because RT-inhibitors can potentially damage normal cells at high concentrations, research is focused on the development of RT-inhibitors that have an acceptable margin of safety.

Suramin and ribavirin are two of the antivirals currently in clinical trials in the United States. There is evidence that suramin has activity against HTLV-III virus both *in vitro* and *in vivo* [12,13] but no clinical benefit has been shown thus far. In a 6-week study of eight patients at NIH, HTLV-III was cleared from the blood of four patients, but no clinical improvement was noted in any of the patients and the virus returned when the medication was stopped. Similar results were reported in a study of three patients at Walter Reed Medical Center and in a study of 16 patients in France. All patients in the U.S. studies and many of those in the French study

developed toxic reactions including rash, proteinuria and pyuria, elevated liver transaminases and hepatitis, and burning sensations of the extremities. This drug has been used on an investigational basis for many years to treat trypanosomiasis and onchocerciasis.

Ribavirin has shown some activity against HTLV-III *in vitro*.[14] In one trial in New York, 27 asymptomatic gay men with HTLV-III infection received an oral formulation of ribavirin in varying dosages. RT activity in cultures of peripheral blood lymphocytes decreased but was not eliminated during treatment. Dose-related side effects included: anemia, nausea, flatulence, headache, fatigue, dry mouth, mental status changes, and dyspnea on exertion. Other studies are ongoing.

Alpha-interferon, a leukocyte-derived protein with antiviral, immunomodulatory and anti-cancer properties, has been shown to inhibit HTLV-III replication *in vitro*. When given to patients with AIDS and Kaposi's sarcoma, about half of the patients had some evidence of reduction in tumor burden, although in many patients the response was transient. More data are needed to determine whether the agent contributes to improved overall survival. Studies are ongoing at Massachusetts General Hospital.[15,16]

In studies abroad, two other antivirals, phosphonoformate (also called PFA or Foscarnet) and HPA-23, have shown some activity against the AIDS virus *in vitro*. PFA is also known to have activity against several herpesviruses, which commonly cause severe and protracted secondary infections in patients with AIDS. Clinical trials of PFA in viremic patients with ARC or AIDS are under way in Denmark and Sweden. The major known side effect of PFA is nephrotoxicity.[13] It is also retained in bone tissue for long periods.

In French studies, HPA-23 has been shown to reduce or clear virus transiently from the blood in some cases. However, no clinical improvement was noted in the 19 patients (7 ARC and 12 AIDS) studied. Viremia reappeared after discontinuation of therapy. Thrombocytopenia, bleeding and hepatic dysfunction are common side effects of this drug[15,16] and are dose-limiting. FDA has approved limited clinical trials of HPA-23 in patients with AIDS. Those trials will begin this fall in five U.S. medical centers.

Another substance, compound BW A509U, a thymidine analogue, has shown *in vitro* activity against HTLV-III. Clinical trials with BW A509U have also been approved and are in progress at Duke University and NIH.

Both HPA-23 and BW A509U have been designated orphan drugs for the treatment of AIDS after application for this status was made by Rhone-Poulenc Pharmaceuticals in the case of the former, and Burroughs Wellcome Co. in the case of the latter. An orphan designation is a way of facilitating early testing of drugs and biologics for rare diseases, including AIDS, by providing tax credits, grants and exclusive approval protection as authorized by the Orphan Drug Act.

Another antiviral agent being considered for investigational use in U.S. patients with HTLV-III is ansamycin, a drug used experimentally in this country to treat *Mycobacterium avium intracellulare* infections, a common opportunistic infection in AIDS patients. (See December 1982 *Drug Bulletin*.) Ansamycin has been shown to have *in vitro* activity against HTLV-III/LAV. In addition, widespread screening of chemicals for activity against HTLV-III/LAV has identified several other compounds which are being readied for clinical trials.

In evaluating these agents, FDA is considering separately their potential effectiveness in asymptomatic carriers of HTLV-III, in ARC and PGL, and in frank AIDS, as it is possible that some agents useful in one may not be useful—and could even be detrimental—in the others.

IMMUNE STIMULATORS

A central component of the immune system, the T-4 lymphocyte, is infected and destroyed by HTLV-III. Because many of the functions of the helper/inducer (T-4) lymphocyte are carried out through soluble protein messengers normally produced by the human body, such as interleukin-2 (IL-2) and gamma interferon, these substances are among those being investigated in the treatment of patients with AIDS.

Based upon the observations of PHS scientists in early 1982 that IL-2 was capable of enhancing the killer cell activity of lymphocytes from AIDS patients, initial clinical trials of this compound began in June 1982.[17] Preliminary results indicate that IL-2 can enhance the lymphocyte count and cause a minor reduction in size of KS tumors in some patients. But neither of these effects by itself has caused significant clinical improvement in the overall clinical status of AIDS patients.[15]

Trials of gamma interferon at NIH from February 1983 to September 1984, in a wide range of doses, showed no clinical benefits to the 25 patients involved. Therefore, trials to study the immunorestorative properties of gamma interferon in patients with AIDS were discontinued. However, the National Institute of Allergy and Infectious Diseases (NIAID) is currently sponsoring a trial of this compound in the treatment of *Mycobacterium avium intracellulare* infections in AIDS patients at Cornell University.[15]

Other immune modulators under investigation for treating AIDS include isoprinosine and thymopectin. Partially through funding provided by an NIAID cooperative agreement, isoprinosine was studied at St. Luke's-Roosevelt Hospital in New York. The study included a small number of patients with AIDS and related illnesses. This study failed to reveal any clinical efficacy of the drug and showed minimal effects on immune parameters measured *in vitro* from patients with AIDS-related illnesses.[15] Thymopectin, a thymic hormone, is being studied at the University of California at Los Angeles (UCLA) under a cooperative agreement with NIAID.[16]

Immunoglobulin therapy is being investigated in the treatment of AIDS in children. It is a unique feature of pediatric AIDS that the patients' immune systems are destroyed before they have had a chance to develop fully.[15]

Some scientists have speculated that it may prove necessary to use a combination of therapies to treat AIDS. Combination therapy involving immunotherapy and antiviral drugs is under way in a study of three patients with AIDS, all of whom have healthy identical twin brothers. The three AIDS patients are being treated at NIH with a combination of suramin and bone marrow transplantation. A study combining suramin and IL-2 in other patients is being planned.

Treatment of Opportunistic Infections and Malignancies

A number of drugs are under investigation for treating the malignancies and opportunistic infections associated with AIDS. Marketed drugs used to treat PCP include trimethoprim/ sulfamethoxazole and pentamidine isethionate. The latter was approved for use in patients with PCP after receiving support from FDA's Office of Orphan Products Development. (See December 1984 *Drug Bulletin*.) Many of the clinical and laboratory studies of this drug were conducted by CDC and FDA. Other agents under investigation for treatment of PCP include dapsone, trimetrexate and alpha-difluoromethyl-ornithine (DFMO).

Other drugs are being investigated for treating AIDS patients with Kaposi's sarcoma, *Mycobacterium avium intracellulare* (see December 1982 *Drug Bulletin*), cytomegalovirus, *Candida albicans* and *Cryptococcus neoformans*. With a disease as serious as AIDS, it is extremely important that there be a concerted effort by the medical community to develop treatments and preventive measures. FDA is encouraging the development of products for use in treating patients with AIDS and other manifestations of HTLV-III infection through a number of mechanisms. FDA works closely with NIH, manufacturers, and academic scientists in the planning of preclinical and clinical studies of drugs and biologic substances for AIDS. With this joint effort, approval for a newly filed investigational new drug application (IND) can be granted in a matter of days and amendments to the original protocol agreed to by telephone as all parties work together to closely monitor the progress of patients under study. FDA scientists in FDA laboratories on the NIH campus collaborate with other groups involved in AIDS research. They are participating in the *in vitro* screening of antiviral drugs and immune stimulators and in the evaluation of patients on experimental treatments at the NIH Clinical Center. This integration of FDA into the total AIDS effort guarantees that, as was the case with the HTLV-III antibody test, any promising product will get rapid regulatory review and become generally available in the shortest possible time.

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FDA Drug Bulletin

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Special AIDS Issue

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FDA Drug Bulletin

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Other Health Professionals

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Letter From The Commissioner

Dear Colleague:

The AIDS pandemic poses a threat not only to the health of our citizens, but also to the very fabric of our society, as physicians labor to treat desperately ill patients in a sensible, compassionate fashion while striving to protect the public health.

Since FDA first published a *Drug Bulletin* devoted entirely to AIDS in October 1985, the health concerns relating to all manifestations of infection with human immunodeficiency virus (HIV) have continued to grow.

FDA, along with other Public Health Service agencies, recently participated in the Third International Conference on AIDS in Washington, D.C. We trust that the exchange of information from meetings such as this will continue in the months and years ahead as we in the public sector seek to work closely with those in academe, industry and research to contain this pandemic.

According to the late June statistics from the U.S. Centers for Disease Control, in the United States there have been more than 37,000 cases of AIDS, and more than 21,000 of these persons have died. Most of the cases continue to be in the highest risk groups of homosexual/bisexual males and intravenous drug abusers.

However, some new demographics are beginning to emerge. We are seeing a disproportionate number of AIDS cases among blacks and Hispanics. And in New York City, where for the last few years AIDS has been the leading cause of death for men aged 25-44, AIDS is now the leading cause of death in women aged 25-34, the second most frequent cause of death for women aged 35-39, and the third most frequent for women aged 20-24. Nationwide, according to the late June CDC statistics, among persons who have had heterosexual contact with a person with or at high risk for AIDS, there were 158 cases among men and 600 cases among women. Of the 2,555 AIDS cases among women, 50% resulted from IV drug abuse and 29% from heterosexual contact. And it is well to remember that any children these women might bear would be at high risk for AIDS.

But most disturbing is that cases meeting the clinical definition of AIDS are only the tip of the iceberg. PHS estimates that 1-1.5 million Americans are infected with HIV. Although some of these persons may be manifesting symptoms of AIDS-related complex (ARC), most of them do not currently show any outward signs or symptoms of HIV infection. Yet they can infect others.

Projections of these statistics into the future can numb the mind and emotions. But health professionals facing AIDS patients with no hope know that behind the statistics are real suffering human beings.

AIDS is, without a doubt, one of the most devastating infectious diseases the world has ever known. This virulence makes AIDS different from any other public health problem and places special demands on health professionals to educate their patients. Although many health professionals are mainly concerned with primary care, specialized aspects, or research, their high public credibility makes them an indispensable part of any public education campaign.

This second issue of the *FDA Drug Bulletin* on AIDS is part of the PHS effort to keep health professionals informed about the latest information on HIV infection. A major focus in this issue is FDA's role in the government-wide effort to contain the HIV epidemic.

FDA's highest priority in our management action plan is the review of promising AIDS therapies. In addition, we have taken steps to safeguard the nation's blood supply and to encourage the

appropriate labeling of latex condoms for use in preventing HIV transmission.

FDA has approved one drug, zidovudine (formerly called AZT), to treat HIV infection in certain AIDS and ARC patients. The agency approved the first clinical testing of zidovudine within five days of receipt of its sponsor's application. When early clinical tests were promising, FDA approved expansion of clinical trials. This led to FDA approval—within one week—of a treatment protocol allowing wider use of the drug for thousands of people with *Pneumocystis carinii* infections complicating AIDS. All told, the review and approval of the zidovudine New Drug Application (NDA) took only 107 days and clinical studies of only 22 months.

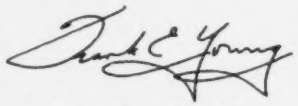
FDA scientists continue to meet frequently with manufacturers of other promising therapies. In addition, we will award contracts to support research focused on aspects of HIV infection directly relevant to the approval process. Instead of merely waiting for applications to appear on our doorstep, we are strengthening our science base and actively working with public and private research groups to develop promising therapies and vaccines and to make them available as soon as possible.

To safeguard the blood supply, FDA has worked closely with private firms in developing test kits to screen for HIV antibody. As a result, FDA approved the first test kit within 10 weeks of its submission to FDA. There are now several test kits on the market and, most recently, we approved a Western blot to be used as an additional, more specific blood test for HIV antibodies. FDA is now working with researchers on the very difficult problem of developing a sensitive test that might directly detect the viral antigen or virus in the blood to eliminate the problem of lag between infection and presence of antibodies.

Most recently we have modified our procedures to enable desperately ill patients to gain early access to innovative drugs where there is no alternative therapy. This investigational new drug procedure should be of value to many physicians.

These are just a few of the many issues that will continue to challenge us in the days—and, I'm afraid, years—ahead. Thus, I want to reiterate my pledge to you that FDA will continue to give the evaluation of products for the treatment and prevention of this disease our highest priority. Furthermore, we will continue to keep the medical community apprised of the latest developments regarding HIV and AIDS.

Sincerely yours,



Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

AIDS Acronyms

AIDS—Acquired immunodeficiency syndrome.

ARC—AIDS-related complex.

HIV—Human immunodeficiency virus. Previously called HTLV-III or LAV.

SIV—Simian immunodeficiency virus. A virus related to HIV and seen in monkeys.

HIV-2—A second form of HIV which has not been seen in the United States. A few cases have been identified in Africa, Brazil, France, West Germany, and Great Britain.

OI—Opportunistic infection.

PCP—*Pneumocystis carinii* pneumonia. A common opportunistic infection in AIDS patients.

KS—Kaposi's sarcoma. A malignant tumor common in AIDS patients.

MAI—*Mycobacterium avium intracellulare*. An avian type of tuberculosis, commonly producing disease in chickens or swine, but rarely in humans other than AIDS patients.

CMV—Cytomegalovirus. An OI that can cause blindness and be fatal in AIDS patients.

LAS—Lymphadenopathy syndrome. A frequent symptom complex seen in HIV-infected patients.

ELISA or EIA—Enzyme-linked immunosorbant assay. Used to screen blood for HIV antibodies.

WB—Western blot. An additional, more specific blood test for HIV antibody; used to validate seropositive reactions to EIA.

CDC—Centers for Disease Control.

MMWR—Morbidity and Mortality Weekly Report. A CDC publication that frequently contains information on HIV.

NIH—National Institutes of Health.

PHS—Public Health Service. The parent agency of CDC, NIH, and FDA (and other agencies). A component of the Department of Health and Human Services (DHHS).

Precautions For Health Care Professionals

Although HIV is not transmitted through casual contact, the potential for transmission always exists when there is contact with body fluids. Recent reports of transmission of HIV from infected patients to health care workers[1] emphasize the importance of routinely taking all PHS-recommended precautions.

The concentration of virus in body fluids is proportional to the number of white cells in the fluid. Therefore, HIV concentrations are highest in blood and semen, somewhat lower in vaginal secretions, and significantly lower in saliva and tears.

ALL INVASIVE PROCEDURES

CDC has published recommended precautions for health care workers involved in invasive procedures.[2] Because the antibody status of most patients will not be known, the recommendations, summarized below, apply to *all* patients:

- All health care workers who perform or assist in invasive procedures must wear gloves when touching mucous membranes or non-intact skin of all patients, and use other appropriate barrier precautions when indicated (e.g., masks, eye coverings, and gowns, if aerosolization or splashes are likely to occur). In the dental setting, as in the surgical and obstetric settings, gloves must be worn for touching all mucous membranes and changed between all patient contacts. If a glove is torn or a needlestick or other injury occurs, the glove must be changed as promptly as safety permits and the needle or instrument removed from the sterile field.
- All health care workers who perform or assist in vaginal or cesarean deliveries must wear surgical gloves and use other appropriate barrier precautions when handling the placenta or infant until blood and amniotic fluid have been removed from the infant's skin.
- After use, disposable syringes and needles, scalpel blades, and other sharp items must be placed in puncture-resistant containers for disposal. To prevent needlestick injuries, needles should not be recapped, purposefully bent or broken, removed from disposable syringes, or otherwise manipulated by hand.
- If an incident occurs during an invasive procedure that results in exposure of a patient to the blood of a health care worker, the patient should be informed of the incident, and previous recommendations for the management of such exposures[3] should be followed.

DENTISTRY

Dental health workers are in professional contact with a large number of patients, most of whom appear to be healthy. However, because a large proportion of persons infected with HIV do not show signs of infection, it is urgent that dental health workers take measures to protect themselves as well as their patients from HIV transmission. A recent report at the International Conference on AIDS, of a dentist who frequently practiced without gloves and who apparently contracted HIV from a patient, emphasizes the importance of following infection control procedures.

CDC has published infection control recommendations for dental health workers that may serve to prevent transmission of HIV as well as other microorganisms. Dentists and others in dentistry are urged to refer to the complete recommendations referenced[4] at the end of this article. Summarized, they include:

Gloves

- Gloves must always be worn when touching blood, saliva, or mucous membranes; when touching blood-soiled items, body fluids or secretions, as well as surfaces contaminated with them; and when examining all oral lesions.
- All work must be completed on one patient, where possible, and the gloves removed and the hands washed and regloved before performing procedures on another patient.
- Repeated use of a single pair of gloves is *not* recommended, since such use is likely to produce defects in the glove material that will diminish its value as an effective barrier.
- Hands must be washed between patients (following removal of gloves), after touching inanimate objects likely to be contaminated by blood or saliva from other patients, and before leaving the operatory. During use, gloves may become perforated, whether or not the operator is aware of it. This allows viral contamination as well as allowing bacteria to enter and multiply beneath the glove material. For many routine dental procedures, hand washing with plain soap appears to be adequate. For surgical procedures, an antimicrobial scrub should be used.

Protective Masks and Gowns

- Surgical masks and protective eyewear or chin-length plastic face shields must be worn when splashing or spattering of blood or other body fluids is likely, as is common in dentistry.
- Reusable or disposable gowns, lab coats, or uniforms must be worn when clothing is likely to be soiled with blood or other body fluids. If reusable gowns are worn, they may be washed, using a normal laundry cycle. Gowns should be changed at least daily or when visibly soiled with blood.

Instruments and Surfaces

- Impervious-backed paper, aluminum foil, or clear plastic wrap may be used to cover surfaces that may be contaminated by blood or saliva and that are difficult or impossible to clean and disinfect. These coverings should be removed (while gloved), discarded, and then replaced (after ungloving) with clean material between patients.
- Instruments that penetrate soft tissue and/or bone should be sterilized after each use. Instruments that are not intended to penetrate oral soft tissue or bone but that may come into contact with oral tissues should also be sterilized after each use if possible; however,

if sterilization is not feasible, the latter instruments should receive high-level disinfection.

- Metal and heat-stable dental instruments should be routinely sterilized between uses by autoclaving, dry heat, or chemical vapor.
- Routine sterilization of handpieces between patients is desirable. In the case of handpieces that cannot be sterilized, other complete cleaning and disinfection procedures should be followed. The same is true of ultrasonic scalers and air/water syringes.
- Because water retraction valves within the dental units may aspirate infective materials back into the handpiece and water line, these valves should be replaced with a non-aspirating method of coolant water containment.

EYE CARE PROFESSIONALS

Although the level of HIV in tears is low and there has been no documented instance of HIV transmission by this fluid, transmission is theoretically possible. Therefore, eye care professionals are advised to take appropriate precautions, including wearing gloves when possible, sterilizing or disinfecting instruments, and disinfecting contact lenses (see October 1985 *Drug Bulletin*).[5]

DIALYSIS

Patients with end-stage renal disease who are undergoing maintenance dialysis and who are infected with HIV or who have AIDS, can be dialyzed in hospital-based or free-standing dialysis units using conventional infection-control precautions. Standard strategies for disinfection and sterilization are sufficient to prevent transmission of HIV.[6]

Clinicians should be aware that the rate of false reactive EIAs in chronic dialysis patients was 4% in one study,[7] much higher than the falsely reactive rate for blood donors (0.17%). When confirmed by Western blot, the rate of truly reactives was 0.8%. CDC is carrying out further studies to assess the prevalence of HIV among chronically dialyzed patients.

OTHER RECOMMENDATIONS

Practitioners interested in other recommendations about preventing HIV transmission are referred to the October 1985 *Drug Bulletin* and previous issues of *Morbidity and Mortality Weekly Report*.[3,8-10]

The compiled *MMWR Recommendations and Guidelines* (Nov. 1982-Nov. 1986) are available through the National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161; phone (703) 487-4650. It is available either as an individual publication (order #87-903399) or as a subscription (order # PB87-903300). The cost is $13.95 plus $3 postage for the 1982-86 compilation. Those ordering a subscription will be billed $6.50 for each subsequent guideline.

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Counseling Patients About Prevention

FDA is urging that physicians and other health professionals help educate patients about ways to prevent the spread of HIV. It should be stressed to patients that because AIDS is a sexually transmitted disease (STD), sexual abstinence or a mutually monogamous relationship with an uninfected partner is the best insurance against acquiring the disease (except when one partner is an intravenous drug abuser, in which case mutual monogamy offers no protection).

CONDOMS

For sexually active persons, the only instance when condoms are unnecessary for reduction of infection risk is within a long-standing, mutually monogamous relationship in which neither partner uses IV drugs and neither partner is infected with HIV. This applies to any sexual activity where the exchange of semen and/or blood is possible, including vaginal, anal, and oral sex.

Recent studies reported in the press have indicated that natural membrane condoms are not able to contain—and, therefore, are unable to protect against infection from—the HIV virus. Therefore, FDA allows only latex condoms to be labeled for the prevention of STDs, including AIDS.

Because the diameter of the HIV virus is about 1/25th that of spermatozoa, there was initially some question about whether condoms could contain the virus. Subsequently, however, *in vitro* tests of latex condoms at the University of California at San Francisco[1] and epidemiologic data[2,3]

confirmed that the HIV virus does not pass through an intact latex condom.

To maximize protection against STDs, it is important that condoms be used properly. FDA sent a letter to all U.S. condom manufacturers, importers, and repackagers regarding the labeling of condoms for prevention of STDs. The letter stated that only latex condoms could be labeled for the prevention of STDs, including AIDS. FDA does not allow natural membrane condoms to be so labeled because they have a different permeability than latex and may not lend themselves to the same degree of uniformity. However, regardless of the product's labeling and composition, FDA requested that all condoms contain adequate instructions for use to maximize the degree of protection they afford.

The Agency suggested the following as an acceptable labeling statement for latex condoms:

"When used properly, the latex condom may prevent the transmission of many sexually transmitted diseases (STDs) such as syphilis, gonorrhea, chlamydial infections, genital herpes, and AIDS. It cannot eliminate the risk. *For maximum protection, it is important to follow the accompanying instructions*. Failure to do so may result in loss of protection. During intimate contact, lesions and various body fluids can transmit STDs. Therefore, the condom should be applied before any such contact."

In its letter to manufacturers, FDA provided the following example as an acceptable set of instructions:

- Use a condom every time you have sexual intercourse or other acts between partners which involve contact with the penis.
- Put the condom on after the penis is erect and prior to intimate contact, because lesions, pre-ejaculate secretions, semen, vaginal secretions, saliva, urine, and feces can contain sexually transmitted disease (STD) organisms.
- Place the condom on the head of the penis and unroll or pull it all the way to the base.
- Leave an empty space at the end of the condom to collect the semen. Remove any air remaining in the tip of the condom by gently pressing the air out towards the base of the penis.
- If a lubricant is desired, use water-based lubricants such as _____. *Do not use oil-based lubricants*, such as those made with petroleum jelly, mineral oil, vegetable oil, or cold cream, as these may damage the condom.
- After ejaculation, carefully withdraw the penis while it is still erect. Hold onto the rim of the condom as you withdraw so that the condom does not slip off.
- Store condoms in a cool, dark, dry place.
- If the rubber material is sticky or brittle, discolored, or obviously damaged, do not use it.
- Do not reuse condoms.

INFORMATIONAL MATERIALS

Government and private agencies have developed a number of informational materials that health professionals may want to have on hand to help answer patients' questions.

Up to 50 free copies of the following materials, produced jointly by PHS and the American Red Cross, can be obtained from AIDS, Suite 700, 1555 Wilson Blvd., Rosslyn, VA 22209:

- Poster featuring Patti LaBelle with Toll-free AIDS hot line number.
- Leaflets:

  AIDS, Sex and You

  Facts About AIDS and Drug Abuse

  AIDS and Your Job—Are There Risks?

  Gay and Bisexual Men and AIDS

  AIDS and Children—Information for Parents of School Age Children

  AIDS and Children—Information for Teachers and School Officials

  Caring for the AIDS Patient at Home

  If your Test for Antibody to the AIDS Virus is Positive. . .

In addition, PHS has developed the following materials:

- Surgeon General's Report on AIDS (October 1986) from AIDS, PO Box 14252, Washington, DC 20004 (up to 50 free copies)
- Facts About AIDS from AIDS, Suite 700, 1555 Wilson Blvd., Rosslyn, VA 22209 (up to 50 free copies)

Up to 25 free copies of the following scriptographic booklets are available from the Office of Public Inquiries, CDC, Bldg. 1, Room B-63, 1600 Clifton Rd., Atlanta, GA 30333:

- What Everyone Should Know About AIDS (also available in Spanish)
- Why You Should Be Informed About AIDS (for health care workers)
- What Gay and Bisexual Men Should Know About AIDS
- AIDS and Shooting Drugs

The following videotapes may be purchased for $55 each from the National Audiovisual Center, 8700 Edgeworth Dr., Capitol Heights, MD 20743-3701; Attn: Customer Service. They may also be borrowed free from Modern Talking Picture Service, 5000 Park St. North, St. Petersburg FL 33709; Attn: Film Scheduling:

- AIDS: Fears and Facts (for the general public)
- What If the Patient Has AIDS? (for health care workers)
- AIDS and Your Job (for policemen, firemen, and other emergency personnel)

Practitioners may want to inform patients of the number of the AIDS toll-free national hot line: (1-800) 342-AIDS, and may want to check with the local health department regarding local hot lines.

References:

1. Conant M et al: Condoms prevent transmission of AIDS-associated retrovirus (letter). *JAMA* 255(13):1706, 1986.

2. Fischl MA et al: Evaluation of heterosexual partners, children, and household contacts of adults with AIDS. *JAMA* 257(5):640-644, 1987.
3. Mann J et al: Condom use and HIV infection among prostitutes in Zaire (letter). *N Eng J Med* 316(6):345, 1987.

Drug Treatment

While no cure has been found for AIDS, progress is being made in developing anti-viral, immune modulating, and biological agents to treat AIDS.

FDA designates all anti-AIDS investigational new drugs (INDs) and new drug applications (NDAs) "1-AA," giving them top priority review to ensure evaluation of the application within 180 days of FDA review time.

ZIDOVUDINE

Zidovudine (formerly known as azidothymidine or AZT) is the first drug therapy approved for the treatment of patients with AIDS. FDA's review and approval of this product took less than four months—one of the shortest approval actions on record. The Agency's giving it top priority and working closely with the manufacturer from the early IND phase made this speedy review possible.

A thymidine analog, zidovudine is an inhibitor of the *in vitro* replication of some retroviruses, including HIV.

Marketed as Retrovir by Burroughs Wellcome, the drug is approved for the management of certain adult patients with symptomatic HIV infection (AIDS and advanced ARC) who have a history of cytologically confirmed *Pneumocystis carinii* pneumonia (PCP) or an absolute CD_4 (T4 helper/inducer) lymphocyte count of less than 200/mm³ in the peripheral blood before therapy is begun.

Specifically, this indication includes HIV-infected patients with one or more of the following disease manifestations:

(1) history of cytologically confirmed PCP regardless of CD_4 count

(2) history of another AIDS-defining opportunistic infection and a CD_4 count less than 200/mm³

(3) advanced ARC characterized by multiple signs and symptoms of HIV infection including otherwise unexplained weight loss (greater than 15 lbs or greater than 10% of prior body weight) and/or recurrent oral candidiasis *and* a CD_4 count of less than 200/mm³. The efficacy and safety of zidovudine have not been adequately studied in patients with AIDS-related malignancies such as KS and lymphomas, in patients with AIDS-dementia complex and/or other neurologic manifestations, or in patients with earlier manifestations of HIV-infection. However, controlled studies of zidovudine are currently under way in all these categories.

Although two double-blind, placebo-controlled trials are generally required for the approval of a drug, the approval of zidovudine was based primarily on the results of one randomized, double-blind, placebo-controlled trial conducted at 12 U.S. medical centers. The study involved 281 patients with AIDS or advanced ARC who were treated for an average of 4½ months. A second study was not required because AIDS is a fatal illness with no other therapy and the results of the first study made it unethical to withhold treatment.

Designed for a treatment period of 24 weeks, the trial was stopped early at the advice of a data safety monitoring board due to a significant reduction in mortality in the zidovudine-treated group. Additional data were collected on about 80% of these patients who received zidovudine in an open-label extension of the trial for an average of five more months. Opportunistic infections and deaths continued to occur in both groups; however, the efficacy of zidovudine in prolonging survival for most patients continued during the additional five months of treatment.

In addition to reducing mortality, results of the controlled trial showed that zidovudine also significantly reduced the risk of acquiring an AIDS-defining opportunistic infection (OI), such as PCP, after the first four to six weeks of treatment. Zidovudine-treated patients generally did better than the placebo group in terms of Karnofsky performance level (ability to perform tasks of daily living), neuropsychiatric function, maintenance of body weight, and the number and severity of symptoms associated with HIV infection. A summary of the data upon which the approval was based has been published recently.[1,2]

Boxed Warning

The labeling of the drug begins with a boxed warning stating that therapy with zidovudine is often associated with hematologic toxicity, including granulocytopenia and severe anemia requiring transfusions. The boxed warning further points out that patients treated with zidovudine may continue to develop OIs and other complications of AIDS or ARC and thus should be under close clinical observation by physicians experienced in diseases associated with HIV.

The Adverse Reactions section of the labeling discusses the occurrence of significant anemia, which in the clinical trial most commonly occurred after four to six weeks of therapy and which in many cases required dose adjustment, discontinuation of therapy, and/or blood transfusions.

In the placebo-controlled trial, although severe headaches were reported more commonly in patients receiving zidovudine than in those on placebo, frank adverse neurologic events were rare. However, in one published report, a patient with advanced AIDS (extensive KS plus multiple opportunistic infections, including PCP, CMV, retinitis, disseminated MAI, and esophageal candidiasis) developed severe headache, unresponsiveness, and focal seizures 48 hours after beginning zidovudine therapy. No structural or metabolic abnormalities were found to explain his condition. Following discontinuation of therapy, he recovered neurologically. Because of the possibility

that multiple drug interactions at the initiation of therapy contributed to the presumed zidovudine toxicity, the drug was reinstituted. Seventy-two hours after rechallenge, the patient developed headache and confusion leading to focal status epilepticus unresponsive to anticonvulsants, and he died.[3]

Drug Interactions

Co-administration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the combination may potentiate toxicity of either drug. During the controlled clinical trial, zidovudine recipients who also took acetaminophen had an increased incidence of granulocytopenia that appeared to be related to the duration of acetaminophen use.

The interaction of other drugs with zidovudine has not been studied in a systematic manner. Co-administration of zidovudine with drugs that are nephrotoxic, cytotoxic, or that interfere with the red blood cell/white blood cell (RBC/WBC) number or function may increase the risk of toxicity. Some experimental nucleoside analogs being evaluated in AIDS and ARC patients may affect RBC/WBC number or function and may increase the potential for hematologic toxicity of zidovudine.

In addition, *in vitro* experiments indicate that ribavirin decreases the activity of zidovudine in inhibiting replication of the AIDS virus when infected cells are exposed to the two drugs simultaneously.[4] Also, there is a published report of neurotoxicity associated with concomitant use of zidovudine and acyclovir.[5]

Patient Information

The labeling contains a section of information that should be communicated to patients. This includes the importance of taking zidovudine exactly as prescribed—every four hours, round-the-clock—even though it may interrupt normal sleep. Physicians are also advised to tell patients that the long-term effects of zidovudine are unknown at this time, and that zidovudine therapy has not been shown to reduce the risk of transmission of HIV to others.

FDA is cooperating with the manufacturer in monitoring a special post-marketing program to compile and analyze extensive data on patients receiving zidovudine on a chronic basis.

POTENTIAL IMMUNO-MODULATING AGENTS

Experimental Treatment	*Sponsor*
Alpha Interferon	Hoffmann-La Roche Inc., Nutley, N.J.
Ampligen	HEM Research, Rockville, Md.
Anti-alpha interferon serum	Advanced Biotherapy Concepts Inc., Los Angeles, Calif.
AS-101	Scientific Testing, Inc., New Brunswick, N.J.
Gamma Interferon	Genentech Inc., San Francisco, Calif.
Immune Globulin IG-IV	Sandoz Pharmaceuticals Corp., East Hanover, N.J.
	Alpha Therapeutics, Los Angeles, Calif.
Imreg-1	IMREG Inc., San Francisco, Calif.
Interleukin-II	Hoffmann-La Roche Inc., Nutley, N.J.
Isoprinosine	Newport Pharmaceuticals, Newport Beach, Calif.
Methionine-enkephalin	National Jewish Hospital, Denver, Colo.
Thymopentin	Ortho Pharmaceuticals, Raritan, N.J.
Thymostimuline	Serano Laboratories Inc., Braintree, Mass.

INVESTIGATIONAL AGENTS

Several potential AIDS therapies are in clinical research. It is important to note that these treatments have not been approved by FDA. However, sponsors have shown that they are sufficiently safe for use in clinical studies.

POTENTIAL ANTI-VIRAL AGENTS

Experimental Treatment	*Sponsors*
AL 721	Matrix Laboratories, New York, N.Y.
Ansamycin	Adria Laboratories, Dublin, Ohio
DDC (Dideoxycytidine)	National Cancer Institute, Bethesda, Md.
Foscarnet	National Institute of Allergy and Infectious Disease, Bethesda, Md.
HPA-23	Rhone-Poulenc, Monmouth Junction, N.J.
Ribavirin	Viratek/ICN Pharmaceuticals, Costa Mesa, Calif.
UA001	Ueno Fine Chemicals Industry Ltd., New York, N.Y.

Information about therapies currently under consideration at FDA is regarded as a trade secret and is therefore confidential and not releasable without consent of the drug sponsor. However, because information about the following therapies has previously been released by the sponsors themselves, FDA can pass this information on to practitioners. Requests for additional information about any of these therapies should be directed to the appropriate sponsor.

References:

1. Fischl MA et al: The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Eng J Med* 317(4):185-191, 1987.
2. Richman DD et al: The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *N Eng J Med* 317(4)192-197, 1987.
3. Hagler DN and Frame PT: Azidothymidine neurotoxicity. *Lancet* (Vol. II):1392, Dec 13, 1986.
4. Vogt MW et al: Ribavirin antagonizes the effect of azidothymidine on HIV replication. *Science* 235:1376, 1987.
5. Bach MC: Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS (letter). *N Eng J Med* 316(9):547, 1987.

Fraudulent AIDS Products

Past experience with health fraud suggests that fraudulent AIDS products may increase as the public becomes more concerned about AIDS.

To help FDA identify such products, health professionals are encouraged to submit examples of questionable AIDS products being marketed directly to the public or to health professionals to: FDA Health Fraud Staff, HFN-304, Center for Drugs and Biologics, FDA, 5600 Fishers Lane, Rockville MD 20857.

Blood And Blood Products

To protect the blood supply from contamination with HIV, in 1983 FDA published recommendations for the deferral of persons at risk for HIV infection and in March 1985 licensed the first in a series of enzyme-linked immunosorbant assays (ELISA or EIA) to test blood and plasma for antibody to HIV.

Donations from persons with a repeatedly reactive EIA are discarded, and these donors are placed on a permanent deferral list. Thus their blood or plasma donations are kept from entering the supply of these products for transfusion or manufacture of blood products. Donors are notified of their antibody status if the EIA is repeatedly reactive and is confirmed by a second, more specific test, such as the Western blot (WB).

FDA recently licensed a WB for validating seropositive reactions to the EIA. Because the EIA is highly sensitive, it results in some nonspecific or false positive reactions. WB is more specific and therefore is an excellent additional test for providing important information about the likelihood that a given test is a false positive or a true positive.

DONOR REENTRY

In conjunction with the WB licensing, FDA sent a memo to all registered blood establishments last April setting out a recommended testing protocol for clarifying the status of blood donors with an unconfirmed reactive EIA who have been permanently deferred from further donation of blood or plasma.

In recommending this protocol, FDA took into consideration that data from two studies indicate that none of the more than 1,000 donors with repeatedly reactive units but with negative WBs were culture-positive for HIV or subsequently showed signs and symptoms of immunodeficiency.

Therefore, FDA recommends that

donors on permanent deferral lists may be reinstated if:

(1) EIAs and WBs on two samples drawn at least six months apart are negative.

(2) the second or most recent WB is performed with a test licensed by FDA.

(3) an EIA produced by using a virus grown in a cell line different from that of the initially repeatedly reactive EIA is also negative on both samples.

To comply with these recommendations, a frozen aliquot of the repeatedly reactive sample that resulted in deferral must be available for testing after a six-month interval. If this sample is not available, the six-month interval period starts when a sample is available for testing and storage.

ALTERNATE TESTING SITES

Beginning in 1985, Federal funds have been available for alternate sites, apart from blood banks, to test persons concerned that they may have contracted HIV.

In addition to removing this burden from blood banks, it was also felt that this would further safeguard the blood supply by providing a place other than blood banks for high-risk individuals to be tested. Alternative sites have been established in all states, the District of Columbia, and U.S. territories.

FDA is expanding the labeling on EIA test kits to include not only its use in screening blood and plasma, but also its use as an adjunct to diagnosis or establishing previous HIV infection.

There have been a number of recommendations recently regarding persons who should seek HIV antibody screening.

In March, PHS advised physicians to consider offering antibody testing to some patients who received transfusions between 1978 and late spring of 1985 (i.e., the period when HIV was being transmitted, but there was no screening of blood). This consideration should be based on the likelihood of infection in the blood recipient and the likelihood of transmission from the recipient. The risk of infection is greatest if the patient received many transfusions and if the blood was collected during the few years before screening in an area with a high incidence of AIDS. Testing is particularly important if the patient is sexually active.[1]

HOW SAFE?

CDC has reported one confirmed case of transmission of HIV[2] from a blood donor despite routine screening for HIV and a case of HIV transmission through transplanted organs.[3]

In the case of blood transmission, the donor's serum tested negative for HIV antibody at the time of blood donations in April and August 1985. But in November 1985, upon subsequent blood donation, he tested positive by both EIA and Western blot. Recipients of the April donation were seronegative, but recipients of the August donation were both seropositive. However, one of the two recipients had other risk factors for HIV infection. The male donor said he had had two homosexual contacts since 1974. He did not consider himself to be at high risk for HIV infection and therefore had not self-deferred.[2]

Since antibody may not be detectable in blood from donors with very recent infections, as in this case, the safety of the blood supply continues to require that persons at increased risk for HIV infection defer themselves.

In the case of transmission via transplanted organs, in August 1986 a cadaveric organ was found positive for HIV antibody by both EIA and WB after some donated organs had been transplanted.[3] A blood sample taken after the donor had received a large number of transfusions had been negative for HIV antibody. Two days later, when the organs were removed, more blood samples were collected and were forwarded with the organs to various transplantation centers. At one of these centers, one of these later samples was found to be seropositive.

Three persons received organs from this donor. Two of them were subsequently found to be seropositive for HIV antibody. The third did not survive the heart transplant procedure.

CDC concluded that the donor apparently was false negative for HIV antibody as a result of the large number of transfusions he received before his serum was collected for testing.[3]

There have been a few reports of HIV seroconversion associated with heat-treated factor concentrates, but all of these occurred with concentrates derived from unscreened blood. No completely documented cases of seroconversions following use of donor-screened, heat-treated products have been identified.[4] FDA is aware of several studies now under way to follow the antibody test results of hemophiliacs who were not previously transfused before receiving donor-screened, heat-treated Factor VIII.

References:

1. CDC: Human immunodeficiency virus infection in transfusion recipients and their family members. *MMWR* 36:137-139, 1987.

2. CDC: Transfusion-associated human T-lymphotropic virus type III/lymphadenopathy-associated virus infection from a seronegative donor—Colorado. *MMWR* 1986; 35:389-391.

3. CDC: Human immunodeficiency virus infection transmitted from an organ donor screened for HIV antibody—North Carolina. *MMWR* 1987; 36(306-308).

4. CDC: Survey of non-U.S. hemophilia treatment centers for HIV seroconversions following therapy with heat-treated factor concentrates. *MMWR* 1987; 36:121-124.

Vaccine Development

Developing a vaccine for AIDS or HIV is likely to be one of the most difficult challenges posed by the AIDS epidemic. FDA coordinated an AIDS Vaccine

Workshop in March to bring together researchers to exchange information and discuss problems and procedures for vaccine development.[1]

Among topics attendees tackled were:

- progress in understanding the pathogenesis of AIDS relevant to vaccine development
- current status of development of candidate AIDS vaccines
- appropriate preclinical testing of candidate vaccines, including current status and application of animal models
- needs for standardization of tests and procedures
- design of clinical trials
- needs for program development for AIDS vaccine evaluation
- potential target populations for clinical trials.

Several factors combine to make the development of a vaccine against HIV particularly difficult. These factors include the high mutability and variability of HIV and the likelihood that it will be necessary to protect against both free virus particles and cells infected with the virus.

TESTING

Clinical trials of candidate vaccines will occur in a series of phases. In phase 1 studies, the objective is to examine initial safety of the vaccine in a small number of low-risk individuals. Parameters measured to assess safety will include tests to detect possible immunosuppression. For this reason, it is likely that even phase 1 studies should be randomized, controlled trials. In phase 2 studies, larger numbers of people at varying risk of HIV infection and in various age groups will be tested. After safety and immunogenicity have been established in phases 1 and 2, large numbers of volunteers at particularly high risk of infection will be studied for vaccine efficacy. The target populations and complexity of the study design will vary depending on the phase of the study.

Ethical concerns can be expected to arise in the course of clinical trials and will need to be carefully addressed. For example, long-term studies in high-risk individuals will need to incorporate educational efforts directed toward AIDS prevention.

FDA expects that clinical trials on one or more vaccines will begin within the year. The agency has developed antibody tests for vaccines and is carrying out these tests for researchers. In addition, special FDA teams have been established to test the vaccines and review data on them when submitted. Nevertheless, it is anticipated that it will be several years, at best, before enough research has been done on any vaccine to qualify it for licensing.

Reference:

1. *Proceedings of AIDS Vaccine Workshop, Vol. I, II; HHS/PHS/FDA*; March 25-27, 1987; National Institutes of Health, Bethesda, Md.

Immunizations For U.S. Children With HIV Infections

Addressing theoretical concerns that vaccination with live, attenuated vaccine viruses may produce serious adverse events in symptomatic HIV-infected children, and that antigenic stimulation might lead to a deterioration of clinical status of HIV-infected children,[1,2] the Immunization Practices Advisory Committee (ACIP) has established recommendations for immunizations of HIV-infected children in the United States.

The complete recommendations were published in the *MMWR* of Sept 26, 1986.[3] The following is a summary of the recommendations for oral polio vaccine (OPV), inactivated polio vaccine (IPV), and vaccines for measles, mumps, and rubella (MMR), bacille Calmette-Guérin (BCG), diphtheria, pertussis, and tetanus (DPT), haemophilus influenzae type B (Hib), influenza, and pneumococcus.

CHILDREN WITH SYMPTOMATIC HIV INFECTIONS

- *OPV, MMR, BCG* and other live vaccines should not be given to children and young adults who are immunosuppressed as a manifestation of HIV infection. These persons should receive IPV and should be excused for medical reasons from regulations requiring measles, rubella, and/or mumps immunization.
- *DPT, IPV, Hib*: The potential benefits of immunization outweigh the theoretical concerns that stimulation of the immune system by immunization with inactivated vaccines might cause deterioration in immune function. Such effects have not been noted thus far among children with AIDS or other immunosuppressed individuals. Immunization with DTP, IPV, and Hib vaccines are recommended, although immunization may be less effective than in immunocompetent children.
- *Flu, pneumococcal vaccines*: As with other conditions producing immunosuppression, annual immunization with inactivated influenza vaccine is recommended for children over 6 months of age, and one-time administration of pneumococcal vaccine is recommended for children over 2 years of age.
- *Immune globulins*: As with other immunosuppressed patients, children with clinical manifestations of HIV infection may be at increased risk of having serious complications of infectious diseases such as measles and varicella and therefore, following significant exposure to these diseases, should receive passive immunization with immune globulin or varicella-zoster immune globulin, respectively.

CHILDREN WITH PREVIOUSLY DIAGNOSED ASYMPTOMATIC HIV INFECTION

- *MMR*: Pending further data, it is recommended that these children be vaccinated with MMR and followed for possible adverse reactions and for the occurrence of vaccine-preventable diseases,

since immunization may be less effective than for other children.

• *OPV*: Available data suggest that OPV can be administered without adverse consequences to HIV-infected children who do not have overt clinical manifestations of immunosuppression. However, because family members may be immunocompromised due to HIV infection, it may be prudent to use IPV routinely to immunize these children.

• *DTP, Hib*: Immunization with DTP and Hib vaccines in accordance with ACIP recommendations is recommended.

CHILDREN RESIDING IN THE HOUSEHOLD OF A PATIENT WITH AIDS

• *OPV*: Children living with others known to be immunocompromised due to AIDS or other HIV infections should not receive OPV because they would be likely to excrete vaccine viruses that would be communicable to their immunosuppressed family members.

• *MMR*: MMR may be given to such a child because extensive experience has shown that live, attenuated MMR vaccine viruses are not transmitted from vaccinated individuals to others.

References:

1. ACIP: General recommendations on immunization. *MMWR* 32:1-8, 13-17, 1983.
2. Zagury D et al: Long-term cultures of HTLV-III-infected T-cells: a model of cytopathology of T-cell depletion in AIDS. *Science* 231:850-853, 1986.
3. ACIP: Immunization of children infected with Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus. *MMWR* 35:595-598, 603-606, 1986.

Change of Address

The *Drug Bulletin* is mailed primarily to health professionals. Requests for mailing label changes should be sent to the appropriate health professional organization. Physicians, for example, should report address changes to the American Medical Association *even if they are not members of that organization*. Write to: AMA, 535 N. Dearborn St., Chicago, IL 60610.

In addition to the AMA, mailing lists for the *Drug Bulletin* are obtained from the following organizations: American Osteopathic Association, American Dental Association, American Pharmaceutical Association, American Academy of Physicians Assistants, American Podiatry Association, and American Hospital Association.

Health professionals who do not belong to one of these organizations and are not receiving the *Drug Bulletin* may be placed on a separate mailing list maintained by FDA. Requests to be placed on that mailing list and changes for that list only (identified by MAILPADB on the label) should be sent to the address below and *a copy of the current label should be included*:

FDA Drug Bulletin
Circulation Dept., HFI-43
5600 Fishers Lane
Rockville, MD 20857

AIDS Education

by Marian Segal

It came quietly to the attention of the medical community six years ago as a curiosity—several puzzling reports of rare illnesses occurring in young homosexual men. It has since erupted into a worldwide epidemic of the disease we now call AIDS.

AIDS—acquired immune deficiency syndrome—had, as of last July, claimed 21,915 lives in the United States alone—more than half of the 38,160 cases reported to the federal Centers for Disease Control since June 1981. Scientists estimate that as many as 1.5 million Americans are now infected with human immunodeficiency virus (HIV—the virus that causes AIDS) and that by the end of 1991, the number of AIDS cases in the United States will rise to 270,000, with 179,000 deaths. Moreover, experts agree that, despite intensive research at top-notch medical institutions all over the world, an effective treatment or vaccine against AIDS will be years in coming.

Dr. Otis R. Bowen, secretary of the Department of Health and Human Services, has said that, "Our best hope today for controlling the AIDS epidemic lies in educating the public about the seriousness of the threat, the ways the AIDS virus is transmitted, and the practical steps each person can take to avoid acquiring or spreading it." (See accompanying article: "Avoiding AIDS.")

In fact, without a cure or vaccine, education is the only game in town, and federal funds for AIDS information and education increase each year. From 1983 through 1986, the Public Health Service spent $40 million on AIDS education. In 1987, $79.5 million will be spent, and President Reagan's 1988 budget requests $103.9 million.

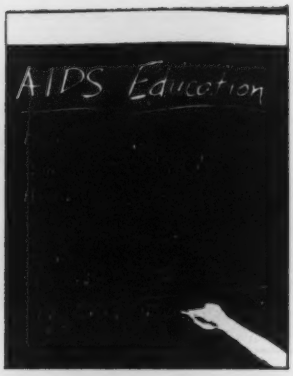
Early public information efforts concentrated on educating high-risk groups and health-care workers about the disease and how it is transmitted. Other early goals were to calm irrational fears and to correct the misperception that AIDS could be contracted through casual nonsexual contact, such as shaking hands or sharing a meal with an infected person.

In the summer of 1983, PHS established a toll-free AIDS information hot line and began distributing a leaflet, "Facts About AIDS," which was revised frequently to provide the most current information on the disease, how it spreads, and how to protect against infection. Videotapes were produced for use by schools, hospitals, community groups, police and fire departments, and others. In early 1986, the American Red Cross and PHS jointly launched a mass media campaign that included television public service announcements, posters, and a series of leaflets providing AIDS information aimed at various segments of the population, such as drug abusers, gay and bisexual men, school officials, parents of school-age children, home health-care providers, and others. In addition, PHS has distributed almost a million copies of the *Surgeon General's Report on AIDS* since last October.

The initial panic has subsided, but a healthy concern about AIDS remains. Continuing media coverage on the growing number of AIDS cases, especially among heterosexuals, has had an impact on people who previously felt themselves out of reach of the deadly virus because they were not in a group "at increased risk" (see box). Although AIDS was first discovered among homosexuals, and gay men still represent the large majority of cases, AIDS is not exclusively a "gay disease"; it strikes men and women, children and adults, and people of all races.

When it comes to prevention, the experts now refer to "high-risk behaviors" rather than "high-risk groups" because *anyone* who practices high-risk behaviors is vulnerable to infection. As Surgeon General C. Everett Koop has said, "Couples who engage in freewheeling sex these days are playing a dangerous game. What it boils down to is—if you don't know *with absolute certainty* that your sex partner is not infected with the AIDS virus—through sex or through drug use—you're taking a chance on becoming infected." It is important to avoid all risky practices, but Dr. Koop stresses two points in particular:

- The risk of infection increases with increased numbers of sexual partners—male or female.
- The best protection against infection right now—barring ab-



"Couples who engage in freewheeling sex these days are playing a dangerous game."—Surgeon General C. Everett Koop

stinence—is use of a condom. Condoms do not provide 100 percent protection, but, used correctly and consistently, they can reduce the risk. A condom should be used from start to finish during sex with anyone who you're not certain is free of infection.

People who engage in high-risk sexual or drug-related behavior should be tested for exposure to the AIDS virus and counseled so that, if they are infected, they can get medical help and learn what to do to keep from infecting others. People who go for testing should inquire about the confidentiality of test results; anonymous testing is available in most states. State and local health departments, private physicians, and many voluntary AIDS organizations have information about testing.

No one knows whether infection with HIV always leads to AIDS, but 20 percent to 30 percent of infected people develop the disease within five years, and the percentage increases as time passes. Most people now carrying the virus have no symptoms and may not even know they are infected. Yet, anyone who is infected—even those who look and feel completely well—will probably carry the virus for life and be able to transmit it to others.

The federal government is intensifying its efforts to educate heterosexuals about AIDS. Programs to educate gay and bisexual men will continue, but increased emphasis will now be placed on the general public, with particular attention to young people, minorities and women. A concerted effort will be directed to educate blacks and Hispanics—two groups that are disproportionately affected. Although blacks represent only 12 percent of the U.S. population, 25 percent of all people with AIDS are black. Another 14 percent of AIDS patients are Hispanic, while this group comprises only 6 percent of the population. And 8 out of 10 children with AIDS are black or Hispanic.

Although some children with AIDS have been infected through transfusions of contaminated blood or blood products, the vast majority—79 percent—acquired the virus from their infected mothers before or during birth. Most of the mothers were intravenous drug abusers or the sex partners of men at high risk. These cases can be prevented if women who are infected or are at increased risk of infection with the AIDS virus avoid pregnancy until more is known about transmission of the disease to their babies.

In a special initiative to inform young people, the government will provide educators with up-to-date information on AIDS. Teen-agers and young adults typically do not think long or hard about their mortality, yet they are particularly vulnerable to AIDS because many of them are beginning to explore their sexuality and, in some cases, experiment with illicit drugs. Clearly, they must have information about the disease, how the AIDS virus is transmitted, and how to prevent infection.

PHS is working with educators, parents and health groups to develop guidelines for school health education on AIDS and to provide information on the availability of instruction materials and other resources. School boards, along with families and community and parent groups, will determine how best to use this information, with consideration of their own values and concerns. Other projects involve programs for colleges and universities, and for youngsters not in school.

PHS will launch several other AIDS information projects over the next two years, and most will contain components specifically designed to reach teen-agers, young adults, parents, minorities, women, and opinion leaders. These projects include:

- Designing and conducting a national mass media campaign using television and radio announcements, posters, and print ads that can be adapted for use by local communities;
- Setting up a coalition of public and private organizations to exchange information and coordinate education programs; and
- Establishing a clearinghouse to answer requests for accurate, up-to-date information from all segments of the population.

In addition, PHS will continue to operate the AIDS hot line, distribute the surgeon general's report, and work with the press to provide accurate information to the public.

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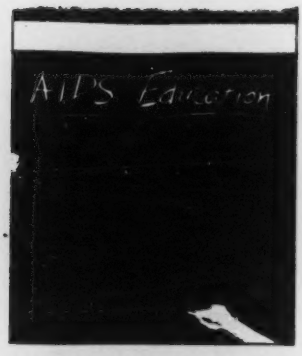

AIDS is perceived now as a threat to the general public by 86 percent of people questioned, and 26 percent are afraid of picking up the virus themselves.

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The crucial question about AIDS education is, "Does it make a difference?" Dr. Walter Dowdle, deputy director for AIDS at CDC, says it does. He points to overwhelming evidence of sexual behavior changes in the gay community, which mobilized quickly and effectively to educate its members about AIDS. "Indirect evidence," says Dowdle, "comes from reports from many cities of 65 percent to 85 percent reductions of sexually transmitted diseases among gay and bisexual men. And there is also evidence that the rate of HIV infection in that hard-hit population is leveling off."

The federal government is continuing to support education and risk reduction programs for gay and bisexual men. These programs include: counseling people who have had, or are considering having, their blood tested for AIDS, and finding ways to change sexual behavior and to reach minority populations at increased risk.

Intravenous drug abusers have been harder to reach through traditional education methods for many reasons, and the government is redoubling its efforts to influence this group. Not only do these drug abusers spread the virus among themselves through sharing contaminated needles, but they are a major source of heterosexual spread of the virus because they can infect their sex partners. The Alcohol, Drug Abuse, and Mental Health Administration is working with public and private health agencies to expand treatment facilities for drug abusers and train staff to provide specialized counseling to accompany AIDS testing. Treatment centers are an important avenue for providing AIDS information, testing and counseling.

What about the impact of education on the general public? There is no doubt that, six years into the AIDS epidemic, almost all Americans (at least 95 percent, according to several polls taken in 1986) know of AIDS. Furthermore, a recent Media General-Associated Press poll of 1,304 adult Americans found that of 44 percent of people who said they feared one disease above others, 48 percent named AIDS as the disease they feared most. Younger people, the survey found, feared AIDS much more than they feared cancer.

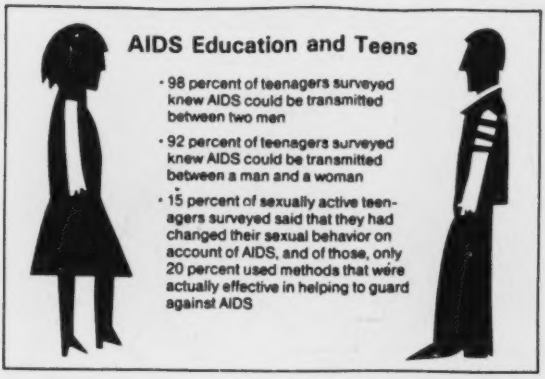
And yet, the results of a survey published in the May 1987 issue of *Pediatrics* revealed that only a small minority of teenagers know what precautions are necessary to avoid transmission of the AIDS virus. Ninety-eight percent of the 860 teenagers (16- to 19-year-olds) interviewed knew the AIDS virus could be transmitted by sex between two men, and 92 percent knew transmission could occur heterosexually. Yet, of the 70 percent of teens who said they were sexually active, only 15 percent reported having changed their sexual behavior because of concern about AIDS. And of those who did change behavior, only 20 percent used effective methods, with only 10 percent mentioning use of condoms. Clearly, this is not good enough.

According to Dowdle, "The impact of education on the general public has certainly been effective in creating a high level of awareness and knowledge among the heterosexual population, but whether a behavior change can be brought about among those who have not lost a friend or loved one to AIDS is not known." Results of a March 1987 ABC News-*Washington Post* survey of 1,511 adults were somewhat more encouraging in that regard. Thirty-seven percent of the people interviewed reported changing sexual behavior to avoid AIDS. Most of the reported changes were effective measures, including having only one sex partner (19 percent), using condoms (11 percent), limiting the number of sex partners (9 percent), and avoiding sex with people with AIDS (8 percent). Eight percent also reported not using drug needles.

And if knowing someone with AIDS motivates people to change behavior, this may provide a greater stimulus in the future as the number of cases rises. Ten percent of people surveyed in the March 1987 poll said they knew someone with AIDS, up from 4 percent of those polled in late 1985. AIDS is perceived now as a threat to the general public by 86 percent of people questioned, and 26 percent are afraid of picking up the virus themselves.

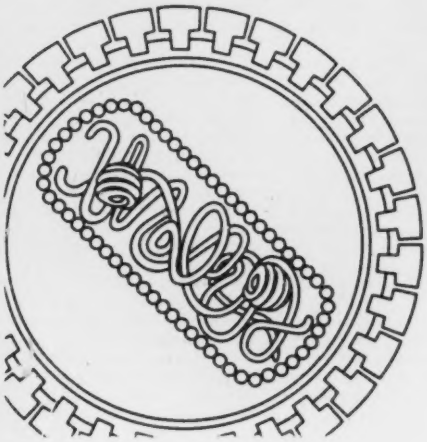
Dowdle says that federal AIDS education programs will be evaluated for both quality and quantity, and that success will be gauged partly by surveys of self-reported changes in behavior and by monitoring the spread of the dread disease. ■

Marian Segal is a member of FDA's public affairs staff.


AIDS Education and Teens
• 98 percent of teenagers surveyed knew AIDS could be transmitted between two men
• 92 percent of teenagers surveyed knew AIDS could be transmitted between a man and a woman
• 15 percent of sexually active teenagers surveyed said that they had changed their sexual behavior on account of AIDS, and of those, only 20 percent used methods that were actually effective in helping to guard against AIDS

Persons at Increased Risk of AIDS

- Men who have had sex with another man since 1977
- People who have shared needles when they inject drugs
- People with symptoms of AIDS or AIDS-related illnesses
- Male or female prostitutes and their sex partners
- Sex partners of people infected with the AIDS virus or at increased risk of infection
- People with hemophilia who have received clotting factor products
- Infants of high-risk or infected mothers ■



How to Get AIDS Information

For more information on AIDS, call the Public Health Service's toll-free hotline: 1-800-342-AIDS.

Free copies of the following materials can be obtained by writing to: AIDS, Suite 700, 1555 Wilson Blvd., Rosslyn, Va. 22209.

- *Surgeon General's Report on Acquired Immune Deficiency Syndrome*—Explains what AIDS is, how AIDS is and is not spread, and what steps people can take to avoid infection with the AIDS virus.
- *Facts About AIDS*—Provides current AIDS information in question-and-answer form. Includes Public Health Service recommendations for preventing transmission of the AIDS virus.
- Color poster, "Get the Facts," features singer Patti LaBelle and provides toll-free Public Health Service hot line number.

Free copies of the following cartoon-style booklets are available from: Office of Public Inquiries, Centers for Disease Control, Building 1, Room B-63, 1600 Clifton Road, Atlanta, Ga. 30333.

- *What Everyone Should Know About AIDS* (also available in Spanish)
- *Why You Should Be Informed About AIDS* (for health-care workers)
- *What Gay and Bisexual Men Should Know About AIDS*
- *AIDS and Shooting Drugs* ■

(Continued)

Avoiding AIDS

Here's what everyone should know to protect themselves and others from AIDS:

AIDS is contagious, but not in the same way that measles or chicken pox or the common cold is contagious. It is a sexually transmitted, blood-borne disease that spreads from one person to another these ways:

- By sexual intercourse between a man and a woman or between two men. The virus can be spread through vaginal, anal or oral sex.
- By sharing needles or "works" used to inject drugs.
- By an infected woman to her baby during pregnancy or delivery, and possibly through breast-feeding.
- By transfusion of infected blood or blood components, although this risk has been sharply reduced by screening procedures for blood and blood donors and new ways to process blood components used to treat clotting disorders, such as hemophilia.

Many people infected with the AIDS virus have no symptoms and may look and feel completely well for many years. But these people can transmit the virus to others, probably during their entire lifetime. And a person can become infected after just a single exposure to the virus.

The AIDS virus (human immunodeficiency virus, or HIV) does *not* spread through casual social contact. In six years of tracking and studying AIDS, scientists have found no evidence that HIV is spread casually through contact at school or on the job, by sharing meals or office equipment, or by handshakes or hugs with an infected person. There is no reason to avoid ordinary social contact with a person with AIDS.

There is no risk of getting AIDS by giving blood; new equipment is used for each donor.

AIDS is not spread by sexual intercourse between two people who maintain a sexual relationship exclusively with each other and who have not been previously infected.

The U.S. Public Health Service recommends that people take these precautions to reduce the risk of exposing themselves or others to the AIDS virus:

- The best protection against sexually transmitted infection by the virus is, of course, to abstain from sex or to have a mutually monogamous relationship with an uninfected person. Avoiding sex with people who have AIDS, people who have tested positive for the AIDS virus antibody, or people at increased risk of infection would also eliminate the risk of sexually transmitted infection.
- If you're not sure that your sex partner is not infected, avoid contact with his or her body fluids. (Body fluids include blood, semen, urine, feces, saliva, and vaginal secretions.)

  —Use condoms, which will reduce (but not eliminate) the possibility of transmitting the virus.

  —Avoid practices such as anal intercourse that may injure body tissues.

  —Avoid oral-genital contact.

  —Avoid open-mouthed, intimate kissing.
- Do not have sex with multiple partners. The more partners you have, the greater your risk of infection.
- Do not use illegal intravenous drugs. If you do, don't share needles or syringes.

If you think you may be infected, or if you have engaged in high-risk sexual or drug-related behavior:

- Seek counseling and a medical evaluation. Consider taking the AIDS antibody test, which would enable you to know your status and protect yourself or—if you are infected—your sex partner.
- Do not use illegal intravenous drugs. If you do, don't share needles or syringes.
- Don't donate blood, plasma, body organs, other body tissues, or sperm.

If you are a woman at increased risk, seriously consider delaying plans for pregnancy until more is known about AIDS and transmission of the AIDS virus. A pregnant woman infected with the AIDS virus has a 30 percent to 50 percent chance of passing the virus on to her unborn child. Women at increased risk of AIDS should take the antibody test before deciding to become pregnant.

For people who have received a positive result on the AIDS antibody test:

- See a doctor. Either avoid sex or tell your prospective sex partner your AIDS test result and take the precautions listed above to protect him or her from infection.
- Inform anyone whom you may have exposed to the AIDS virus—through sex or drug use—of their potential exposure, and encourage them to seek counseling and antibody testing.
- Don't share toothbrushes, razors, or other items that could become contaminated with blood.
- If you use drugs, enroll in a treatment program. Never share needles and other drug equipment.
- Do not donate blood, plasma, sperm, or other body tissues or organs.
- Tell your doctor, dentist and eye doctor that you are infected with the AIDS virus so that proper precautions can be taken to protect you, them and others.
- Women with a positive antibody test should avoid pregnancy. ■

FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available. Talk Papers are not intended for general distribution outside FDA, but all information in them is public, and full texts are releasable upon request.

T88-47
June 22, 1988

Brad Stone
(301) 443-3285

MONTHLY UPDATE ON EXPERIMENTAL AIDS THERAPIES AND VACCINES:

INACTIVATED POLIO VACCINE CLINICAL TESTING GIVEN PERMISSION TO BEGIN

Since the publication of the last month's AIDS Therapies and Vaccines supplementary Talk Paper T88-39 (May 18, 1988) the following AIDS development has occurred:

FDA has granted permission, with some modifications, to an investigational new drug application for the clinical testing of inactivated polio vaccine as a treatment for AIDS. Connaught Laboratories, Inc., of Swiftwater, Pa., the distributor of inactivated polio vaccine, will sponsor the clinical trials.

Although the vaccine is approved for the prevention of polio, its use for any other indication, including the treatment of AIDS, has not been substantiated by scientifically derived data. But since some researchers have theorized that polio vaccine might in some way bolster the immune system's ability to ward off the AIDS virus, FDA has consented to the sponsor's desire to conduct clinical testing of the vaccine in order to simply resolve this question.

-MORE-

Under the terms of the approved protocol for clinical testing, the company will sponsor a study in 30 patients with AIDS who are unable or unwilling to take Retrovir (commonly known as AZT). The randomized, controlled clinical studies will be conducted by Dr. Glenn Mathisen at the LAC-Olive View Medical Center at Sylmar, Calif.

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Special Communication

The FDA's New Procedures for the Use of Investigational Drugs in Treatment

Frank E. Young, MD, PhD; John A. Norris, JD, MBA; Joseph A. Levitt, JD; Stuart L. Nightingale, MD

The Food and Drug Administration has established new procedures to make promising investigational drugs available for treatment of patients with immediately life-threatening or serious diseases as early in the drug development process as possible and well before general marketing begins. The purpose of this article is to inform the medical community about these new procedures and to facilitate their implementation. Examples of immediately life-threatening and serious diseases are given and the procedures that physicians should use to obtain a drug under the new regulations are described. The treatment use of zidovudine (Retrovir), while still in the investigational phase, is described as a case study. The article also summarizes the Food and Drug Administration's new procedures under which drug sponsors can charge for investigational drugs.

(JAMA 1988;259:2387-2389)

THE DESPERATE situation facing patients with acquired immunodeficiency syndrome (AIDS) has highlighted the need to make promising new drugs available as early as possible in the development process. Because of the need to evaluate drugs to treat AIDS rapidly, the Food and Drug Administration (FDA) has created a special I-AA internal agency designation for AIDS-related drugs to ensure that they receive the highest priority at all stages of the drug-review process. Despite these modifications in the review process for therapies for AIDS and other dreaded diseases, we are concerned that everything possible be done to make not only promising AIDS-related drugs, but also other significant therapies, available to the public as soon as we have enough data to make a reasonable judgment that the drug may be effective and that it will not cause unreasonable risk.

Therefore, the FDA has recently established procedures to make promising investigational drugs that are not yet generally marketed available for patients with immediately life-threatening or serious diseases. We have taken these steps, which include codification of a "Treatment IND" (treatment investigational new drug application), so that breakthrough drugs that are still undergoing clinical trials can be used for patients when there is no satisfactory alternative treatment.

Last year, the FDA formally proposed[1,2] and made final[3,4] the new procedures that outline the circumstances for treatment use, outside of a clinical trial, of experimental drugs. We expect with these procedures not only to facilitate the availability of promising new drugs to desperately ill patients as early in the drug-development process as possible, but also to obtain additional data on the drugs' safety and effectiveness.

In this article, we will describe the new procedures to assist physicians in bringing to their patients important new therapies that are still technically in the investigational stage and provide an overview of the regulation. Additionally, we will explain the practical aspects of how and when to make application to either the commercial sponsor or, less commonly, the agency itself.

PAST PRECEDENTS FOR TREATMENT USE OF INVESTIGATIONAL DRUGS

In some instances in the past, the FDA has encouraged the use of treatment protocols for promising drugs prior to final approval for marketing. Our new Treatment IND procedures are built on experiences with treatment protocols initiated after the basic studies of a drug were well under way and when early clinical evidence appeared strongly favorable. These procedures enabled patients in some cases to be treated with the drugs outside of the controlled clinical trials. The first class of drugs to arouse interest in treatment protocols was the cardioselective β-blockers. Several thousand patients with bronchospastic lung disease received the drug metoprolol outside of controlled trials well before it was approved in 1976.

Similarly, the antiarrhythmic drugs recently approved—tocainide, mexiletine, flecainide, and encainide—were made available to physicians who cared for patients with complex, life-threatening arrhythmias prior to the approval of their New Drug Applications (NDAs). One of these drugs, amiodarone, was approved in late 1985, but before that over 600 cardiologists treated at least 20 000 patients under Treatment INDs. The FDA was able to obtain information from these highly qualified specialists as they treated their patients.

In addition, calcium antagonists, offering a new treatment modality for angina, especially for patients with vasospastic angina, were used widely under treatment protocols. Twenty thousand patients ultimately took nifedipine before approval of the NDA.

From the Food and Drug Administration, Rockville, Md.

Reprint requests to the Office of Health Affairs, Room 14-96, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (Dr Nightingale).

thereby generating significant safety data from follow-up studies. Another calcium antagonist, verapamil, was given to approximately 5000 patients under treatment protocols.

Another example where the FDA successfully utilized the Treatment IND approach is that of somatrem (Protropin), a synthetically derived human growth hormone. A Treatment IND for somatrem was needed when it was recognized that the pituitary growth hormone that was previously supplied was contaminated with Creutzfeldt-Jakob virus and had led to the deaths of several individuals who were treated with this particular compound. This Treatment IND was highly significant because it met the urgent public health need of those American children who depended on this therapy and were at risk of developing life-threatening hypoglycemia.

Other examples over the past decade where special situations have led to treatment availability of investigational drugs include the group C cancer drugs (eg, etoposide and streptozocin [streptozotocin]); a system of distribution has been in effect since the mid-1970s for anticancer drugs deemed sufficiently promising to be made available to patients with cancer through the National Cancer Institute's limited distribution system. Similarly, a program for the treatment availability of tetrahydrocannabinol for treating nausea and vomiting secondary to cancer chemotherapy was established, utilizing the same system. More recently, built on the concept of the Treatment IND, a modified group C procedure was introduced to make interleukin 2 combined with lymphokine-activated killer cells, and interleukin 2 alone, available through experimental studies in comprehensive cancer centers.

CASE STUDY: ZIDOVUDINE

The primary motivation for the codification of the Treatment IND process was the demonstrated need to bring breakthrough drugs to desperately ill patients when no other alternative therapy exists. The extreme plight of people with AIDS clearly exemplifies this need. Thus, zidovudine (Retrovir [formerly called azidothymidine]) illustrates how rapidly an experimental drug can be made available once it appears promising for an immediately life-threatening disease for which there is no effective alternative in early clinical trials.

The first phase of human testing for zidovudine, involving only 28 patients with AIDS and AIDS-related complex, was conducted from July to December 1985. Results of those very limited trials were promising and Phase II trials began in February 1986 to test the drug's safety and effectiveness. Close to 300 patients with AIDS, most of whom suffered from *Pneumocystis carinii* pneumonia, were involved in this multicenter trial,[7] which was a randomized comparison of zidovudine and a placebo. In September, the trials were halted early when it was found that 16 patients taking the placebo had died, whereas only one patient taking zidovudine had died.

Once these impressive data were submitted to the FDA, it took the agency less than a week to grant a Treatment IND to treat AIDS patients with a history of *P carinii* pneumonia. The FDA also approved a model informed consent form as part of an overall effort to facilitate availability of the drug. In all, more than 4000 patients with AIDS were treated with zidovudine between the time that the Treatment IND application was filed in September 1986, the time that the NDA was filed in December 1986, and the date of the approval of the NDA on March 19, 1987. Therefore, of the total 21 months of clinical evaluations and review, the drug was available to physicians throughout the country through Treatment INDs for a period of six months or about 30% of the time required for clinical evaluation and approval of the NDA.

NEW FDA CRITERIA AND PROCEDURES

In our new Treatment IND procedures,[4] we have explained some of the factors that we believe are important considerations in determining whether treatment use of an experimental drug is appropriate and we have outlined how investigational drugs can be obtained for treatment purposes for serious or immediately life-threatening diseases. It should be emphasized that there are very specific criteria that must be met for the treatment use to be approved by the agency.

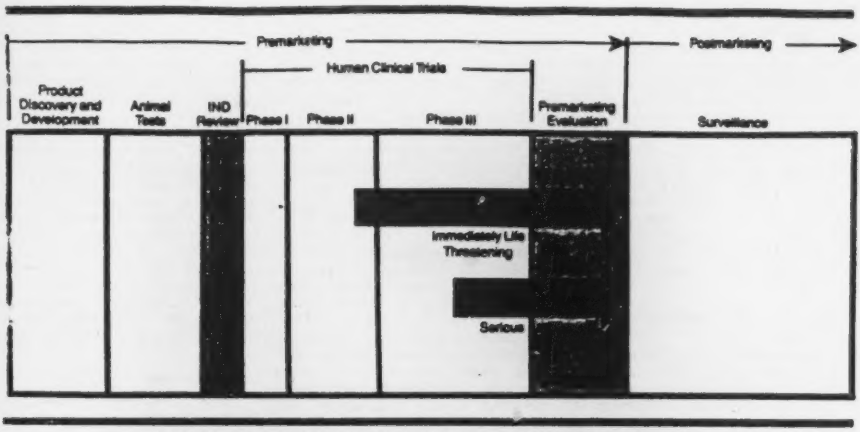
The initial criteria are that (1) the drug is intended to treat a serious or immediately life-threatening disease; (2) there is no comparable or satisfactory alternative or other therapy to treat that stage of the disease in the intended population; (3) the drug is under investigation in a controlled clinical trial under an IND in effect for the trial or all clinical trials have been completed; and (4) the sponsor for the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

For drugs intended to treat an immediately life-threatening disease, a request may be denied for treatment use if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug (1) may be effective for its intended use in its intended patient population or (2) would not expose patients who receive the drug to an unreasonable and significant additional risk of illness or injury. In addition, for drugs intended to treat a serious disease, the treatment use request may be denied if there is insufficient evidence of safety and effectiveness to support such use.

The FDA will generally consider Treatment INDs for drugs in the latter stages of clinical testing, after a critical nucleus of data has become available (Figure). In the case of an immediately life-threatening disease, a drug may be made available for treatment use earlier than Phase III investigations, but ordinarily not earlier than Phase II investigations. In the case of a serious disease, a drug ordinarily may be made available for treatment use during Phase III investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase II investigations. The treatment use of a drug in these circumstances includes the use of a drug for diagnostic purposes. Discussion of the phases of clinical testing is provided in the FDA regulations at 21 CFR §312.21.[8]

In considering the treatment use of experimental drugs, the stage of a disease is important in determining whether it is immediately life threatening, serious, or not serious. For example, for some diseases such as multiple sclerosis, treatment use of an experimental drug would not be appropriate at early stages of the disease. In applying for an investigational drug for a Treatment IND, the sponsor should define the intended patient population and, in medically appropriate cases, limit treatment use to particular stages of a disease or to patients with a particular set of symptoms. For example, as described earlier, the Treatment IND for zidovudine was limited to AIDS patients who had a history of *P carinii* pneumonia.

To illustrate the types of diseases or stages of diseases that would normally be considered to be immediately life threatening, the FDA has provided the following examples in its final regulation: advanced cases of AIDS, advanced congestive heart failure (New York Heart Association class IV), recurrent sustained ventricular tachycardia or ventricular fibrillation, herpes simplex encephalitis, most advanced metastatic refractory cancers, far-advanced em-



Drug development process: treatment use. Drug evaluation process is divided into number of steps. Steps involving Food and Drug Administration (FDA) analysis are shown in shaded portions. Consultation with FDA is encouraged throughout process and strongly recommended at end of Phase II investigations and when application for treatment use of investigational new drug is contemplated by sponsor. The FDA evaluates postmarketing data supplied by both sponsors and physicians. Arrows denote time of onset and duration of use of Treatment INDs for immediately life-threatening and serious diseases.

physema, severe combined immunodeficiency syndrome, bacterial endocarditis, and subarachnoid hemorrhage.

The following would normally be considered serious diseases or stages of diseases: Alzheimer's disease, advanced multiple sclerosis, advanced Parkinson's disease, transient ischemic attacks, progressive ankylosing spondylitis, active advanced systemic lupus erythematosus, certain forms of epilepsy, nonacidotic or hyperosmolar diabetes, and paroxysmal supraventricular tachycardia.

These examples are illustrative only and are not intended as a comprehensive list.

HOW TO GET INFORMATION ON WHICH DRUGS ARE AVAILABLE UNDER TREATMENT INDs

The FDA intends to inform physicians when an investigational drug has been approved for treatment use in an immediately life-threatening or serious disease for a patient population for which there is no satisfactory alternative drug or other therapy available. The FDA will utilize the *FDA Drug Bulletin*, which is mailed without charge to over a million physicians and other health professionals several times a year; the FROM THE FOOD AND DRUG ADMINISTRATION column in *JAMA* (which appears in the second issue each month); and other vehicles, such as press releases and background papers, as appropriate. In the short period since our new treatment-use procedures were announced, we have received a number of applications for a Treatment IND, and three have already been approved: cytomegalovirus immune globulin for attenuation of primary cytomegalovirus infection associated with kidney transplantation, ifosfamide and mesna for germ cell carcinoma where first line and salvage chemotherapy have failed, and trimetrexate for *P carinii* pneumonia in certain AIDS patients. More applications are expected as physicians and pharmaceutical companies become more familiar with our new procedures.

HOW TO APPLY FOR TREATMENT USE OF AN INVESTIGATIONAL DRUG

The goal of the treatment-use procedures for investigational drugs is to make promising drugs available to desperately ill patients earlier than they would otherwise be available, while still enabling the clinical trials to progress. It should be emphasized that the FDA is setting up flexible rather than rigid procedures. The FDA will consider the specific situations on a case-by-case basis and the Commissioner will evaluate all evidence as a whole before making a final decision. A physician may follow two pathways to obtain drugs for desperately ill patients. The most efficient and recommended path is through contacting the commercial sponsor of the investigational drug so that the sponsor of a drug within a controlled trial can make the drug available under a treatment protocol, if the sponsor has not already done so. The less-preferred path is for the physician to contact the FDA directly. This will be necessary only when the commercial sponsor of the investigational drug is unwilling to offer a treatment protocol.

Requesting the Drug From a Sponsor

The physician should directly contact the sponsor (most frequently a pharmaceutical company, but occasionally a government agency such as the National Institutes of Health). The sponsor will make available a brochure containing technical information for appropriate use of the drug by the practitioner. The sponsor will also make available to the physician the drug itself. The sponsor will have on file with the FDA information that includes (1) the intended use of the drug; (2) an explanation of the rationale for use of the drug, including, as appropriate, a list of what available regimens ordinarily should be tried before using the investigational drug or an

explanation of why the use of the investigational drug is preferable to the use of available marketed treatments; (3) a brief description of the criteria for patient selection; (4) the method of administration of the drug and the dosages; (5) a description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk; (6) an informational brochure for supplying to each treating physician; and (7) a commitment by the sponsor to ensure compliance of all participating investigators with the informed consent and Institutional Review Board requirements of 21 CFR parts 50 and 56.[6]

Requesting the Treatment IND Directly From the FDA

If a physician wants to obtain an investigational drug subject to a controlled clinical trial for a treatment use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a treatment protocol.

If the sponsor of the controlled clinical investigation of the drug has not gained approval for or will not apply for a Treatment IND for the drug, a physician may seek to obtain the drug from the sponsor and personally submit a Treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. A Treatment IND request from a physician must include (1) a signed form FD 1571, the Investigational New Drug Application; (2) a statement of the steps taken by the practitioner to obtain the drug under a treatment protocol from the drug sponsor; (3) a treatment protocol containing (a) the intended use of the drug, (b) an explanation of the rationale for use of the drug, including, as appropriate, a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments, (c) a brief description of the criteria for patient selection, (d) the method of administration of the drug and the dosages, and (e) a description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk; (4) a statement of the practitioner's qualifications to use the investigational drug for the intended treatment use; (5) the practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug; and (6) a statement to the effect that the investigator agrees to report safety information to the FDA in accordance with the FDA's regulation 312.32.[7] The FDA will review Treatment IND applications and respond to the physician within 30 days.

OTHER ASPECTS OF TREATMENT IND USE

To best protect the patient, the FDA is instituting a number of important modifications of current practice. One ensures that drugs distributed under a Treatment IND or treatment protocol are manufactured in adequate facilities to ensure quality control. The FDA will take special precautions to guard against health fraud and any other inappropriate use of a drug that has not completed all phases of evaluation and review. Additionally, the FDA does not want to jeopardize the controlled clinical trials that are under way. Thus, the procedures make authorization of a Treatment IND or treatment protocol contingent on the existence of ongoing clinical trials and on the drug sponsor's active pursuit of marketing approval. The FDA is committed to ensuring that the Treatment IND process does not create disincentives to the expeditious development and approval for marketing of promising therapies. Obviously, these decisions require the exercise of judgment by the Commissioner on a case-by-case basis.

In this context, we emphasize the importance of introducing "orphan drugs" to the market. The FDA's Orphan Drug program will continue to emphasize the need to develop and make available orphan drugs for individuals with rare diseases. Efforts will be made to accommodate patients with such diseases within the Treatment IND context. Additionally, physicians should know that the FDA will continue to respond on a case-by-case basis to requests for emergency INDs for individual patients. Need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the drug for a specified use in advance of submission of an IND. A request for such authorization may be transmitted to the FDA by telephone or other rapid means of communication. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor's submitting an appropriate IND as soon as practicable after receiving the authorization.

The FDA's new procedures contain a number of other important elements. For example, they define conditions under which drug manufacturers may charge for investigational new drug products. These conditions are intended to provide sufficient incentives for drug manufacturers to make investigational new drugs available to patients before general marketing begins, but under sufficient safeguards to prevent commercialization of the product, as well as to ensure the integrity of clinical trials.

CONCLUSION

The FDA has developed a number of innovative procedures in an effort to bring hope to thousands of desperately ill Americans and their families. The FDA plays a critical role in improving the quality of health care in this country. While those in the academic and governmental research communities are engaged in the initial discovery and clinical testing of new therapeutic agents, it is the FDA's role and responsibility to facilitate the swift transfer of new discoveries from the laboratory into the marketplace. Only then can important new therapies serve their true purpose of helping patients. The FDA has no higher priority than facilitating the timely availability of important, safe, and effective new drug products to treat desperately ill patients.

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6. 21 CFR parts 50 and 56.
7. 21 CFR 312.32.

The CHAIRMAN. We have our next witness, Dr. Anthony Fauci, the AIDS coordinator at the NIH. Dr. Fauci is not a stranger to this committee. We have previously had Dr. Fauci before us to describe the NIH efforts against AIDS.

We look forward to his testimony.

STATEMENT OF DR. ANTHONY S. FAUCI, DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD

Dr. FAUCI. Thank you, Mr. Chairman.

The CHAIRMAN. We will put your whole statement in the record here.

Dr. FAUCI. I want to thank you for the opportunity to present to you the progress made by the National Institute of Allergy and Infectious Diseases in its efforts to identify and evaluate promising treatments for AIDS and its sequelae.

As you mentioned, I have given my full written statement to you, and now I will outline and summarize some of the salient features of it. I will not speak about the early screening and targeted drug development programs which were alluded to by other speakers, but I would be happy to answer questions on them.

I will go very quickly to the fact that you and your staff have asked us the specific question of how we decide which drugs should enter into clinical trials within our AIDS Clinical Trials units in order to understand the process whereby time is taken for a drug to go from one step to another.

There are many claims of promising drugs, some scientifically founded, others totally unfounded. We have developed a mechanism to help us decide, based on scientific data, which are the most promising and in what order of priority to place them.

Thus, we have established the AIDS Clinical Drug Development Committee—or the ACDDC—to evaluate candidate drugs for entry into NIAID sponsored clinical trials. The membership is composed of both government and nongovernment experts in clinical trials, including representatives of the AIDS Clinical Trials Group, or ACTG, to provide continuity.

Drugs may be submitted from a number of sources, including industry, academia, and government. For each drug, the Committee provides a detailed review and recommends whether that drug should enter a clinical trial, and with what priority. Their recommendations are based primarily on laboratory or clinical data which suggest that a drug may be effective in some aspect of the treatment of HIV infection. On occasion, a drug may be recommended for evaluation solely on the basis that it has achieved some level of widespread use among persons with AIDS. This has been the case with AL-721. For the most part, decisions are made by the committee immediately. The only time a decision is not rendered immediately is when additional information is needed. For example, the ACDDC may recommend additional safety and efficacy studies in animals.

Once a drug is recommended for clinical study, it enters our national network of AIDS Clinical Trials Units—or ACTUs—which is collectively referred to as the AIDS Clinical Trial Group (ACTG).

Within this system, the development of a clinical trial to study that drug follows a very well-established course. An idea or concept for a study may be proposed by an investigator, a pharmaceutical firm, or NIAID staff and referred to the appropriate ACTG committee which has specific expertise relevant to that drug. Each committee includes membership taken from the Units, and is organized along the lines of specific disciplines of AIDS research; for example, opportunistic infections; oncology; pediatrics. Each committee is responsible for developing the research agenda, namely, the studies that should be undertaken; setting the priority among these studies; and monitoring their progress; essentially shepherding the drug through the clinical trial.

It is important to point out that the initiation of clinical trials with investigational new drugs is often complicated and requires extraordinary coordination among Government, research institutions, and pharmaceutical manufacturers. At either the stage of the ACDDC review of a drug, or the drug's subsequent referral to the ACTG committee, there are often a variety of issues that still may need to be resolved. There is the development of the study strategy for the evaluation of a particular drug, and the development of a protocol to fit that strategy. Extensive negotiations with the manufacturer are often needed to ensure the production of sufficient quantities of clinical grade material prior to the further development of the protocol. All supporting preclinical information, manufacturing processes, and proposed trial design must be approved by the FDA. The pharmaceutical manufacturer must agree to supply the drug required to conduct the study, as well as agree with the design of the protocol. Institutional Review Boards at the individual medical centers must also review and approve the proposed protocol. Case report forms must be designed and reviewed with statistical input to assure that the measurements being taken throughout the study are being collected in a manner that will provide the necessary data to meet the predetermined objectives. And finally, patients must be screened in order to select the population that meets the intended protocol entrance criteria.

While this approach may appear to be heavily burdened with reviews and approvals by committees, these steps ensure that resources are spent most efficiently; that the studies are carried out in a scientifically sound manner; and, most importantly, that the results are interpretable.

Now, I want to make it very clear that we empathize with and understand, the desire of persons with AIDS and individuals infected with HIV to be on a clinical trial. I and several members of my staff have been taking care of AIDS patients virtually every day since 1982 and we are aware of their concerns.

It is important, however, to point out that the major goal of the process that we're talking about is to definitively determine whether a drug is safe and effective so that it can ultimately be made available to all who would benefit from it. Or on the other hand, if it proves to be unsafe or ineffective, we must get it out of use so that it will not harm people or divert them from being included on studies of potentially useful and safe drugs. We are constantly fine tuning the system to move this process along more quickly without compromising science.

Nonetheless, despite the number of steps involved in the process it certainly is not business as usual. I am pleased to report that the number of investigational new drug applications and protocols submitted to the FDA has increased significantly in the past six months compared with the first 18 months of the program, and we have submitted this information to you through your staff. With the evolution of the program and the process, we now are beginning to see an increased momentum in activity that I am confident will continue.

Although there were already indications of increased momentum, to assure that the program was performing at an optimal level, I appointed an AIDS Clinical Trials Advisory Group in the summer of 1987 to review the progress of the program and to offer recommendations for the future. This committee, made up predominantly of nongovernment scientists, issued its report in December of 1987. The Group stated that the successful development of this program in such a short period of time, and under an extreme degree of public and political scrutiny, represented an assignment of enormous proportions unprecedented in clinical research in this country. This view is also reflected in the President's Commission report. In short, the panel believed that a great deal had been accomplished and was impressed by the overall function of the program. Nonetheless, they made a number of recommendations for strengthening the program. Some of these have already been adopted, and the rest are being implemented. We take these recommendations very seriously.

In order to have greater involvement in the direction of our clinical trials program by the participating extramural investigators, we merged our original AIDS Treatment Evaluation Units with the grant-supported AIDS Clinical Studies Groups to form a single cooperative group known as the AIDS Clinical Trial Group. We believe that this cooperative arrangement is encouraging a sense of partnership and providing a creative environment with greater incentives—and most important, flexibility—for new approaches to the design and the implementation of protocols.

The program is relatively young. As recently as one year ago, there were only 10 staff involved with the AIDS drug development and clinical trials. Despite this, substantial progress has been made, and at a rate unprecedented in NIH experience with clinical trials. At present, 39 protocols have been started, involving approximately 4,000 volunteers. Although AZT has been an important drug under study, approximately 18 others have entered clinical trials, including six antivirals, five drugs for opportunistic infections, five immunomodulators, and two anti-neoplastic drugs. In addition we are also studying many drug combinations.

While much has been achieved, much more needs to be done. We are continuing to make changes to increase the effectiveness of the program. In this regard we have met frequently with representatives of constituency groups and others to share ideas and solicit input regarding the direction of the program. As a result of this open dialogue, we are increasing the linkage between the clinical trials program and standard patient care.

The first such step will be a new program to involve community physicians in clinical research so that they may participate in the

study of new drugs as early as possible. Most patients with HIV infection are cared for in the community setting, that is, under the care of a private practitioner or providers not affiliated with academic institutions. This is especially true for IV drug abusers and for people with asymptomatic infection.

We are enthusiastic and see many opportunities presented by the Community Clinical Research Program, or the CCRP. However, we also must recognize that there are issues we must resolve in order to implement it. Many community physicians are not experienced in the development of research plans, and may require more than the usual assistance in preparing grant applications. We are willing to provide this. In addition, we are aware of a variety of administrative issues, such as the fact that the established NIH funding mechanisms currently do not allow the support of individuals; rather they traditionally support organizations with administrative structures. Thus, we have the responsibility to ensure that administrative and business issues are resolved and not ignored.

As a first step, we will be meeting this summer with community representatives to discuss the various options for this initiative to discuss the needs, research interest, and capabilities of the community providers.

The CHAIRMAN. Why in the world—you say this is the first step. You've been meeting with these people all along. Why in the world are you saying it is the first step this summer.

Dr. FAUCI. We have been meeting with them——

The CHAIRMAN. Well, why is this the first step then? What have you been doing? You talk with these people all the time?

Dr. FAUCI. Actually to formalize the plans for getting official RFAs issued and research grants out to them.

The CHAIRMAN. Well, what in the world have you been doing down there? You have been coming up here and testifying here and over in the House. And now we are going to have the first meetings this next summer.

Dr. FAUCI. No, the first meetings are not this next summer, Mr. Chairman. We have been meeting with the constituency groups all along.

The meeting this summer is going to solidify a number of meetings that have been going all along actually to draw up plans so that we can award grants for these individuals. I don't mean at all to imply that this is the first time we've met with them.

The CHAIRMAN. Are you going to give grants as a result of the meeting?

Dr. FAUCI. We cannot give grants as a result of the meeting.

The CHAIRMAN. I don't understand. I won't spend any more time. But solidify procedures in order to give grants sounds very—maybe that has a profound meaning with regard to the agency, but it sounds like doubletalk to me.

Dr. FAUCI. What I mean, Mr. Chairman, is that if a group that has very little experience in submitting grants submits a grant, the chances of that grant being put together in a manner that would result in a meaningful study are somewhat limited. We have been dealing with the constituency groups. We have already made a commitment in our Fiscal Year 1989 budget to put aside money for

the CCRP. And we will be trying to help them develop grants in a form that will favorably be judged in peer review.

The CHAIRMAN. Let me just go—we have a conflict, I do, at quarter of. Senator Weicker will chair the remainder of the hearings. But I want to just inquire.

You are providing these concept sheets, as I understand it now, to us as a result of our questions; is that true?

Dr. FAUCI. Yes, we are.

The CHAIRMAN. I would like to see if we cannot regularize so we can monitor that over the period of time. Try to get it every four or five months.

Dr. FAUCI. I would be happy to do that, Mr. Chairman.

The CHAIRMAN. Now you testified earlier in the year, in April, according to the Times story, "A top Federal health official said today the clinical trials of several promising AIDS drugs had been delayed for as much as a year because of insufficient staff to guide each drug through the testing process." Dr. Fauci said that lack of personnel was "almost exclusively" the reason why several high priority drugs have not yet entered clinical trials. This was the first admission by any top Federal health official that failure to commit enough resources has slowed the development of AIDS treatment.

And then we saw on June 29th the story in the Washington Post, headlined "Bush Endorses AIDS Antibias Efforts." It says in that story, "[Vice President] Bush told reporters he did not favor an immediate increase in federal research funds because Dr. Anthony S. Fauci of the National Institutes of Health told him at a dinner at his home two nights ago that the funding allocated to NIH for that purpose now is about 'right.' "

Which is right?

Dr. FAUCI. Well, with regard to the first question, I was addressing the number of FTEs, or full-time equivalent employees, involved in AIDS research. At that time, I had made a request for a certain number of FTEs to fill a variety of needs, including clinical trials; and in fact, I didn't get as many as I asked for.

Since that time Dr. Wyngaarden has given us for this Fiscal Year an additional five FTEs for drug development clinical trials, and in 1989, 37 additional FTEs for this purpose. Those 5 FTEs for the remainder of 1988 will allow us to hire 20 new staff for clinical trials.

Thus far, we have now added seven, and we have seven more in various stages of the hiring process. So things are moving along more quickly for a number of reasons, including the fact that we now have more FTEs than were originally allocated to us.

With regard to the budget, that is a complex question when one thinks about can you use——

The CHAIRMAN. Well, before we leave that, so you've got how many more now? You said it was a lack of personnel that was the almost exclusive reason why several high priority drugs have not yet entered clinical trials.

Under the number of FTEs now that you have, will there be any high priority drugs that will not get clinical trials?

Dr. FAUCI. There are a number of reasons why a high priority drug might not get into a clinical trial. But I am almost certain

that, with the current and projected FTEs for drug development and evaluation, a high-priority drug that does not have another compelling reason for not getting into a clinical trial, such as the company not wanting to put it in one of our trials—which is the case with a couple of drugs—will get into a clinical trial.

The CHAIRMAN. Then both statements as far as you're concerned are accurate, both the testimony about clinical trials, and that prominent AIDS drugs have been delayed as much as a year because of insufficient staff.

Now with the new numbers, you said, what again?

Dr. FAUCI. Five this year and 37 in 1989 for a total of 42 additional in drug development and clinical trials.

The CHAIRMAN. And when did they come aboard?

Dr. FAUCI. Immediately after the hearing, Dr. Wyngaarden gave me 5 FTEs, which, as I mentioned, really equals 20 employees because we're so far into the fiscal year. We also have a promise of an additional 37 FTEs for fiscal year 1989.

The CHAIRMAN. When are the 37 coming in?

Dr. FAUCI. The 37 will come in fiscal year 1989.

The CHAIRMAN. Well, is that soon enough?

Dr. FAUCI. Right now, the way you get people on board, Mr. Chairman, it would be almost impossible to get 37 people on board between now and the beginning of the year.

The CHAIRMAN. Can you get any? Are you recruiting any now?

Dr. FAUCI. Yes, we have. We already have recruited 7, and 7 are getting ready to come on board, for a total of 14 since that time.

The CHAIRMAN. And does that complete the need?

Dr. FAUCI. With the additional 37 next year for the drug development and clinical trial component of it, yes.

The CHAIRMAN. We need to have some idea in terms of the priorities. Obviously, we do not want to throw money at it, but we also want to support those. We cannot support it if we do not know about what the needs are.

You know, we mentioned earlier the confidential memoranda that was requested and which mentioned the figures of the $755 million, which is if you are able to have all the things that you really wanted and that could be justified; and then we had the request going down by $422 million for the request of the Congress.

Just in fairness to both the American people, on the one hand, if someone said: Look, if we really want to do the job, this is what we need; these are the resources we need, and we are getting it from people who are researchers, scientists, clinical specialists, those that probably have the best kind of background and research capability to make that decision. Then we come up to about 422. It was increased modestly with the action by the House and Senate.

We are clearly falling short, are we not, in terms of those recommendations that were made to the White House?

Dr. FAUCI. Those recommendations of the 790——

The CHAIRMAN. We can put the chart back up.

Dr. FAUCI. Yes. I certainly do not know where you got that chart, but I will try to see if I can——

The CHAIRMAN. Yes, I will ask the staff.

Did you mention to George Bush that that was about right?

Dr. FAUCI. I am on record at the House Appropriations Subcommittee and the Senate Appropriations Subcommittee of saying that, for what we need to do in the coming year, the $588 million request is about right. Now, obviously if you ask scientists whether or not they can use more money, they certainly will always be able to say they can use more money. But given the total picture of the budget, we feel we would be able to mount a good effort with the $588 million that is in the budget right now for 1989.

The CHAIRMAN. The only point is, Dr. Fauci, that this is—you know, we either think it is a national health emergency or we do not. If there is not a scientific basis for those kinds of research that the scientists ask about, it should not be approved. But all of us know that there are many which are or should be approved from a scientific point of view, but there is not adequate funding for it. This is the question, whether it meets that particular scientific threshold.

If it does and we think this is a national emergency, the American people think we ought to expend it. That is clear, I think, to anyone. You know, your Gallup poll will show you that. We want to know what we are missing out on.

Do you have the copy there? I do not want to take a lot of time. Did they hand you that?

Dr. FAUCI. Yes, they did. But let me just address——

The CHAIRMAN. Do you recognize it?

Dr. FAUCI. Yes, I do. Let me address your first comment, if I might, with your permission, Mr. Chairman. I certainly consider the AIDS epidemic a national emergency. It occupies virtually all of my time. I am, in addition to being the Coordinator of AIDS Research for the NIH, the Director of the National Institute of Allergy and Infectious Diseases. As you know very well from your dealings with us, this institute is responsible for allergies, immunology, transplantation, vaccines, sexually transmitted diseases, tropical medicine, malaria, et cetera, et cetera. Forty-one percent of our budget is AIDS; 41 percent of a budget that includes asthma, allergy, sexually transmittal diseases, transplantation, tropical medicine, et cetera. So I certainly take it very, very seriously.

The CHAIRMAN. I am not arguing that there are some not robbing Peter to pay Paul either. We have seen a lot of that type. I mean, I am sure it is justified. I will take your word, certainly, for it in that agency, but we have also seen a lot of moving around as well.

Dr. FAUCI. This table, which was prepared late in 1986 in response to the Institute of Medicine (IOM) report "Confronting AIDS" shows our Fiscal Year 1988 request to OMB, which was $285 million. The "additional" column is the result of Dr. Wyngaarden's request to the institutes for their requirements in meeting the IOM recommendations, to utilize the Nation's biomedical research capacity optimally. The additional amount submitted for 1988 was $404 million, bringing the total to $750 million. I must stress that the Institute submissions were never reviewed within NIH to eliminate duplications or projects that were just not feasible for that year—for example, certain Institutes included money to prepare for a Phase III vaccine trial, which is not feasible since we are barely into Phase I trial. I would also stress that this table does not

represent a budget exercise; it was merely a professional judgment response to the IOM report and was never used in the development of our AIDS budget.

The CHAIRMAN. Let me just ask this. You are the professional. I will not personally accept pie-in-the-sky. You have got professional people making recommendations. It might be your assessment they are pie-in-the-sky.

Let me go down the list. "More beds at the clinical center." Do you need more beds at the clinical center? Yes or no?

Dr. FAUCI. Right now the Cancer Institute is requesting more beds to do inpatient research.

The CHAIRMAN. "An animal research facility," they requested "more funds to develop standardized reagents," "expanded NIH fellowship training programs," "a centralized AIDS research databasing clearinghouse," "vastly increased funds for behavioral research," "funds/authority to hire nurses and senior biomedical researchers," "funds/authority to hire senior administrative managers."

That does not sound like pie-in-the-sky to me.

Dr. FAUCI. No, it is not pie-in-the-sky, and several of those areas that you have just mentioned have already been addressed and are being addressed, for example, the beds in the Clinical center as well as the centralized data facility. So I do not consider that pie-in-the-sky either.

The CHAIRMAN. Would you go back to the treatment IND? We talked a little bit about that with Young, and I think you heard what we were talking about. Can you speak to that issue?

Dr. FAUCI. I believe the point that you had made, your main point with regard to your questioning of Dr. Young, was the difference between "may be effective" and something definitively showing that a drug is effective before it is given out under a treatment IND. And I know there is a great deal of discussion and controversy about that. But the way the regulation reads right now is that it must be shown to be effective. If the regulation were changed and it were just safety, then I guess more patients could receive some sort of treatment under that. That is something that is out of my area. That is a regulatory not a research area. But I understand the question that you were asking, and it was with regard to the appropriateness of requiring definitive effectiveness before a drug goes out under a treatment IND.

The CHAIRMAN. Well, I guess a little later we are going to hear from a witness who feels the NIH has been a little too choosy about the drugs that it is willing to put into clinical testing. Realistically, Dr. Fauci, would it be a bad idea to get some quicker answers for a few more of these drugs even if they are dark horses?

Dr. FAUCI. Well, we certainly want to get answers as quickly and as expeditiously as possible. I described for you the process whereby a drug goes into a clinical trial. It gets scrutinized by members of the various committees, which are predominantly made up of outside investigators with expertise in clinical trials. The ones that, in fact, are judged to look like there would be a good chance of something happening, or even a reasonable chance of getting a positive result, we get into clinical trials as quickly as possible.

What often happens is that a drug may get touted as being promising in the newspapers, and then when you look at the data and you scientifically scrutinize them, there is no reason at all to believe that the drug would have any effect in vivo. Unfortunately, that information does not get out to the public, and the public sometimes is misled when they read in the newspapers that something is promising.

The CHAIRMAN. Well, Dr. Young is saying he needs the drugs to review in order to use the treatment IND. What can you tell us about what NIH is going to do to speed up that?

Dr. FAUCI. Well, as soon as we get a drug that is at a point in a clinical trial where it looks like it is safe and has indication of efficacy, we are very much in favor of moving that right into a treatment IND.

The CHAIRMAN. And you do not have a limitation of resources, personnel, that you did have last April in terms of being able to effectively evaluate those and speed up and get a greater number of drugs over there moving?

Dr. FAUCI. Dr. Wyngaarden and I meet on a continuing basis, Mr. Chairman, to reassess those needs. Right now with the 37 that are promised to me in 1989 and the 5 I have received in 1988, that appear to be enough. If the situation changes and more drugs come along than we now anticipate to move it, then I certainly would ask for more personnel.

The CHAIRMAN. Well, we will be monitoring this closely both with you and Wyngaarden and with the companies and the other researchers, as well as the others who are following, hopefully in a constructive and positive way what is happening at the Institute.

I want to thank you very much. We might have some further questions I might submit. I am very grateful to our colleague, the Senator from Connecticut, who has been such a leader on this whole issue, for being willing to chair the remainder of the hearing.

Dr. FAUCI. Thank you. I appreciate being here.

[The prepared statement of Dr. Fauci follows:]

STATEMENT BY

ANTHONY S. FAUCI, M.D.

DIRECTOR

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

July 13, 1988

FOR RELEASE UPON DELIVERY

Mr. Chairman and members of the Committee, it is a pleasure for me to be here today to discuss the progress made by the National Institute of Allergy and Infectious Diseases (NIAID) in its efforts to identify and evaluate promising treatments for the acquired immunodeficiency syndrome (AIDS) and its related sequelae.

An effective and comprehensive clinical trials effort is required to identify the best possible therapies to control this epidemic. The program which we established in 1986 at the NIAID, in collaboration with other Institutes, has evolved very rapidly and today is providing a mechanism for the scientifically sound evaluation of currently available candidate therapies for AIDS.

Before I describe the current system for the clinical evaluation of drugs, I would like to provide some general background information on drug development that may be useful:

Before most drugs are evaluated for clinical safety and efficacy against the AIDS virus, they will have come through a comprehensive development program. This program employs two basic approaches: (1) the screening of already existing compounds to determine their effectiveness against the human immunodeficiency virus (HIV) or (2) targeted drug development using the information gained about unique properties of HIV to design new agents that interfere with the life cycle or structural components of the virus.

The goal of the AIDS screening and preclinical drug development program is to discover and develop expeditiously the most promising anti-HIV agents for clinical testing. The anti-HIV activity of AZT, the first and, at present, the only drug approved for use in AIDS, was discovered through the National Cancer Institute's (NCI) efforts in screening drugs in the test tube. The NCI's program currently is examining approximately 120 unique compounds weekly for anti-retroviral activity. Thus far, the screen has identified 45 compounds with definite anti-retroviral activity. This program is complemented by the NIH Intramural Structural Biology Program and by the NIAID network of National Cooperative Drug Discovery Groups (NCDDGs), whose purpose is to focus on targeted development of drugs. These latter Groups represent a coordinated effort to use the capabilities of academic institutions, pharmaceutical companies, biotechnology and bioengineering companies, and international organizations, in cooperation with the Federal Government, to develop anti-HIV drugs. Over the past year several hundred drugs have been analyzed. Out of the NCDDG-AIDS program, three new drugs -- CS-87, D4T, and soluble T4 -- have been identified by NCDDG investigators and are currently undergoing preclinical development by Triton Bioscience, Bristol Myers and Biogen, and SmithKline Beckman, respectively. All three of these new drugs are likely to be in clinical trials by winter of next year.

Rather than commit valuable resources on unpromising drugs, we have developed a mechanism to help us decide which are the most promising; namely, to prioritize. To accomplish this, we established an AIDS Clinical Drug Development Committee (ACDDC) to evaluate candidate drugs for entry

into NIAID-sponsored clinical trials. The membership is composed of both Government and non-Government experts, including representatives of the AIDS Clinical Trials Group (ACTG). We believe that the inclusion of the ACTG representatives provides continuity and has enabled us to move the drugs more quickly into clinical trials. Drugs may be submitted from a number of sources including industry, academia, and Government. For each drug, the Committee provides a detailed review and recommends whether that drug should enter a clinical trial, and with what priority. Their recommendations are based primarily on laboratory or clinical data which suggest that a drug may be effective in some aspect of the treatment of HIV infection. Our goal is that any drug that has shown scientific promise and receives a high priority rating will be evaluated in a clinical trial. On occasion a drug may be recommended for evaluation solely on the basis that it has achieved some level of widespread use among persons with AIDS. For the most part, decisions are made by the Committee immediately. The only time a decision is not rendered immediately is when additional information is needed. For example, the ACDDC may recommend additional safety and efficacy studies in animals.

Once a drug is recommended for clinical study, it enters our national network of AIDS Clinical Trials Units (ACTUs), collectively referred to as the AIDS Clinical Trials Group (ACTG). Within this system, the development of a clinical trial to study that drug follows a well established course. An idea for a study may be proposed by an investigator, a pharmaceutical firm, or NIAID staff and referred to the appropriate ACTG committee with specific expertise relevant to that drug. Each committee includes

membership taken from the ACTUs and is organized along the lines of specific disciplines of AIDS clinical research (e.g., opportunistic infections, oncology, pediatrics). Each committee is responsible for developing the research agenda, i.e., the studies that should be undertaken; setting priority among these studies; and monitoring their progress. In effect, the committee becomes the advocate for a given drug as it proceeds through the process of a clinical trial.

Some concern has been expressed that there may have been undue delays from the point of the ACDDC designating a drug as "high priority" to its being entered into a clinical trial and patient accrual begun. However, it is important to point out that the initiation of clinical trials with investigational new drugs is often complicated and requires extraordinary coordination among Government, research institutions, and pharmaceutical manufacturers. There are many issues that limit our ability to go rapidly from the designation of a drug as "high priority" to patient accrual into a clinical trial.

At either the stage of ACDDC review of a drug or the drug's subsequent referral to the ACTG committee, there are often a variety of issues that still may need to be resolved: design of a drug strategy and the development of a protocol to fit that strategy; extensive negotiations with the manufacturer are often needed to ensure the production of sufficient quantities of clinical grade material prior to the further development of the protocol(s); all supporting preclinical information, manufacturing processes and intended trial design must be approved by the Food and Drug

Administration; the pharmaceutical manufacturer must agree to supply the drug required to conduct the study as well as agree to the design of the protocol; Institutional Review Boards at the individual medical centers must also review and approve the proposed protocol; case report forms must be designed and reviewed with statistical input to assure that the measurements being taken throughout the study are being collected in a manner that will provide the necessary data to meet the predetermined objectives; and finally, patients must be screened in order to select the population that meets the intended protocol entrance criteria. Once all of the above elements have been addressed, the investigators are permitted to initiate the clinical trial. The failure of any one or more of these elements to be accomplished in a timely fashion can cause unforeseen delays.

While this approach may appear to be heavily burdened with reviews and approvals by committees, it is not. We believe these steps ensure that resources are spent most efficiently and that protocols are carefully developed, requiring a thoughtful process involving both the Government and the investigators conducting the studies. In fact, despite the number of steps involved in the process, I am pleased to report that the number of investigational new drug applications (INDs) and protocols submitted to the FDA has increased significantly in the past six months compared with the first eighteen months of the program. For INDs, the number has increased from 13 in the first eighteen months compared with 8 in the past six months alone; the figures for protocols are 31 and 19, respectively. With the evolution of the program and the process, we are now beginning to see an increased momentum in activity that I am confident will continue.

Although there were already indications of increased momentum, to assure that the AIDS clinical trials program was performing at an optimal level, I appointed an AIDS Clinical Trials Advisory Group in the summer of 1987, to review the progress of the program and offer recommendations for the future. This committee, made up predominantly of non-Government scientists and chaired by Dr. Robert Couch of Baylor College of Medicine, issued its report in December 1987. The Group stated that the successful development of this program in such a short period of time, and under an extreme degree of public and political scrutiny, represented an assignment of enormous proportions, unprecedented in clinical research in this country. In short, the panel believed that a great deal had been accomplished and was impressed with the overall function of the program. Nonetheless, they made a number of recommendations for strengthening the program. Some of these have already been adopted, and the rest are now being implemented.

It should be noted that the Advisory Group concurred with and further expanded the original objectives of the clinical trials program. First, they reaffirmed that the overall goal was to provide an effective and efficient system to evaluate the efficacy and toxicity of therapeutic interventions against HIV infection, including AIDS and its sequelae. They also pointed out that the program must assure that studies address questions of highest scientific priority. Furthermore, the clinical trials program should assume responsibility for developing and testing new drugs up through the stage when they are made available to patients. This includes sponsorship of scientifically meritorious studies intended to support a new

drug application (NDA) and necessitates performing trials at standards that will support approval of the drugs. The basis for this lies in the well established fact that if the studies are not done properly, the data likely will be erroneous and the drugs will not get approved.

In order to have greater involvement in the direction of our clinical trials program by the participating extramural investigators, we merged our original contract-supported AIDS Treatment Evaluation Units (ATEUs) with our grant-supported Clinical Studies Groups to form the single cooperative group now known as the AIDS Clinical Trials Group. We believe that this cooperative arrangement is encouraging a sense of partnership and providing a creative environment with greater incentive for new approaches to the design and implementation of protocols.

In a related matter, we have organized an accelerated process for development of protocols. To free up the ACTU investigators' time from processing details and allow them more time actually to conduct their clinical studies, we have established a contract to provide writing and logistical support to them for developing their protocols. This also has helped expedite the development of the protocols themselves. In addition, we have put into place the new committee structure I described earlier for evaluating treatments within the ACTG. By expanding the range of ideas to be tested, increasing the flexibility in studies, and especially increasing the resources devoted to protocol development, we will be able to accommodate a wider range of studies and potential new AIDS therapies. We have already seen positive results from this change, with 42 concept sheets

(concepts for clinical studies) reviewed since March 1988 alone and 35 new protocols in development in the same time period.

The NIAID AIDS drug development and treatment research program is relatively young. As recently as one year ago, there were only ten staff involved with AIDS drug development and clinical trials. Despite this, substantial progress has been made, and at a rate unprecedented in NIH experience with clinical trials. At present, 39 protocols have been started involving approximately 4,000 volunteers. Although AZT has been an important drug under study, approximately 18 others have entered clinical trials, including 6 antivirals, 5 drugs for opportunistic infections, 5 immunomodulators, and 2 anti-neoplastic drugs. In addition, we also are studying many drug combinations.

While much has been achieved, there is much more to be done. We are continuing to make changes to increase the effectiveness of the program. In this regard, we have met frequently with representatives of constituency groups and others to share ideas and solicit input regarding the direction of the program. As a result of this open dialogue, we are increasing the linkage between the clinical trials program and standard patient care.

The first such step will be a new program to involve community physicians in clinical research so that they may participate in the study of new drugs as early as possible. Most patients with HIV infection are cared for in the "community" setting, that is, under the care of a private practitioner or providers who are not affiliated with academic institutions. This is

especially true for intravenous drug abusers and for people with asymptomatic infection. The enthusiasm of the community providers is an important incentive to our pursuing this initiative, and in addition, we believe that there are a number of scientific opportunities. For example, practitioners have medical concerns that are sometimes not focused upon in the large clinical trials that could be pursued through this effort; systematic collection of data from the actual practice setting could provide useful preliminary information on many popular, but not formally studied treatments; finally, community-based projects could provide the means for studies such as assessing the impact of research on primary care.

Although we are enthusiastic and see many opportunities presented by the Community Clinical Research Program, we also recognize that there are issues we must resolve in order to implement it. Foremost among them is the necessity to mesh the research needs with the capabilities and interests of community providers. Many community physicians are not experienced in the development of research plans and may require more than normal assistance in preparing grant applications. In addition, we are aware of a variety of administrative issues such as the fact that the established NIH funding mechanisms currently do not allow the support of individuals; rather, they traditionally support organizations with administrative structures. Thus, we have the responsibility to ensure that administrative and business issues are resolved and not ignored. To accomplish this may require substantial administrative and technical assistance and resources.

As a first step, we are planning to meet this summer with community representatives to discuss various options for this initiative, to identify the needs, research interests and capabilities of community providers, and finally to work with them in developing the Request for Applications (RFA) which we plan to issue early in Fiscal Year 1989 in order to implement the program next fiscal year. The next step will be to address many of the administrative issues that remain to be resolved.

Regardless of any delays we may experience with the Community Clinical Research Program, we are moving ahead to ensure as best as possible that all populations affected by AIDS have appropriate access to clinical trials. One approach we have taken to accomplish this was the convening of an ad hoc advisory group of minority leaders in science and community affairs to help us improve access to clinical trials for women and minorities and advise us on how to increase involvement of minorities in our outreach and education efforts. I expect to receive the final recommendations from the group later this summer.

Mr. Chairman, this concludes my prepared statement. I will be delighted to answer any questions you may have.

The CHAIRMAN. Thank you very much for that, Senator Weicker.

Senator WEICKER [presiding]. Thank you, Mr. Chairman. I am going to let Dr. Fauci go. I have no questions of him, but I think it should be fairly pointed out that both Dr. Fauci and Dr. Wyngaarden, and others at the National Institutes of Health, have operated really without the wholehearted support of an adminstration, both from the OMB point of view, and that which emanates from the White House—which has been less than enthusiastic in lending weight to their scientific efforts.

In their appearances before the Appropriations Committee, starting four years ago they have not hesitated to speak out on the matters of concern to them as they relate to the HIV virus.

I think it also important to point out that the matter of personnel has been perceived to be a problem by the Senate, and the House has disregarded our advice on this matter. They are not going to disregard it this year because in the hearings before Congressman Weiss, I believe it was, it came out that, very frankly, there were personnel restrictions which impacted on these trials, et cetera.

So there are problems. The administration just has dragged its feet. Certainly Dr. Koop has not; certainly Admiral Watkins has not; certainly Dr. Fauci has not. But the philosophers who have been permitted to have their say have impeded both science and public policy.

As an example of public policy, this famous AIDS mailer that went out should have gone out a year earlier. That was ordered by Senator Chiles and myself two years ago and was held up for one additional year. Now, you tell me how many people contracted AIDS in the meantime.

I might add, public policy could not be where it is today were it not for Senator Kennedy, and he has held the fort at this side while I have done it over on the appropriations side. But I think he is as keenly aware as I am as to the sort of unique difficulties to which the scientific community has been placed during a time of emergency. I am delighted to hear his support for doing whatever is necessary so that some of these roadblocks that have been put up by the administration and by the philosophers will be removed.

I can say this: We would not have any AIDS legislation before us were it not for the very able and human leadership of Ted Kennedy.

I have no further questions, Dr. Fauci.

[Information supplied for the record follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

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JUL 13 1988

The Honorable Edward M. Kennedy
Chairman, Committee on Labor and Human Resources
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

I am writing to inform you of NIH's progress in expediting the review and award of AIDS projects.

In recent months NIH has taken many steps to respond to the urgent need to expedite the review and award of grants, cooperative agreements, and contracts for AIDS research. Beginning with the receipt dates of February 1 and March 1, 1988, for new and competing grant applications, normal referral and review schedules were compressed to about 6 months (from 10-11 months for unsolicited applications and from 7-8 months for solicited). We expect to fund successful February/March submissions during August. Slight variations in contract procedures have enabled us to make those awards within 6 months as well. This timetable meets the requirements of the conference report accompanying the Continuing Resolution for Fiscal Year 1988 (House Report 100-498).

These initial efforts to expedite the review and award process were accomplished by special temporary staff assignments and by adopting revised schedules for the necessary grant scientific review processes and the special Advisory Council/Board review. We are now in the process of recruiting for newly allocated positions to devote to the accelerated review of AIDS projects on a continuing basis.

NIH has taken steps to establish the accelerated review as standard procedure. Special receipt dates have been established for investigator-initiated AIDS research grant applications. In addition to specific requests for applications and proposals, concepts of future solicitations will be announced in the NIH GUIDE FOR GRANTS AND CONTRACTS whenever possible. Prospective applicants may be asked to submit letters of their intent to submit applications or proposals, to facilitate early formation of peer review groups. We have obtained OMB permission to require up to 32 copies of unsolicited and 23 copies of solicited AIDS grant applications, thus enabling NIH to receive sufficient copies immediately for administrative needs. We have asked that institutions include their PHS human subjects certifications and animal welfare verifications with AIDS applications in order to expedite review.

Some members of the research community have expressed concern regarding these new procedures. Some reviewers are unable to take on an even greater burden, and some applicants have requested that their applications not be evaluated via the expedited process. However, we feel that this will happen in only a small number of cases and that we will be able to act on the majority of applications within 6 months of receipt. We hope to be able to award fellowships in 4 months. However, some large-scale projects (e.g., center applications, clinical trials, those involving multiple sites) will of necessity require more than 6 months.

I assure you that NIH is responding to the AIDS crisis with all available resources. We will consolidate the gains we have made in speeding up the review process and establish these new procedures as routine. We feel that this will enable us to respond effectively, without sacrificing the quality of the review of AIDS projects and the quality of the science.

Sincerely,

William F. Raub

for James B. Wyngaarden, M.D.
Director

Senator WEICKER. We have Panel No. 5: Dr. John Beary, senior vice president for Science and Technology, Pharmaceutical Manufacturers Association; Dr. Barry Gingell, director of the Medical Information, GMHC, Inc.; and Dr. Marcus Conant, professor of Dermatology, University of California, San Francisco.

Gentlemen, why don't you go ahead and proceed? I have to leave here in ten minutes, and Senator Stafford is arriving and he only has a few minutes. What I would like you to do, if you can, is to submit all your statements for inclusion in the record in their entirety. And if you could, try to synopsize the essence of those statements. Proceed in any way that you care to.

STATEMENTS OF JOHN F. BEARY, M.D., SENIOR VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, DC; BARRY D. GINGELL, DIRECTOR, DEPARTMENT OF MEDICAL INFORMATION, GAY MEN'S HEALTH CRISIS, INC., NEW YORK, NY; AND MARCUS CONANT, M.D., PROFESSOR OF DERMATOLOGY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, CALIFORNIA STATE DEPARTMENT OF HEALTH AIDS LEADERSHIP COMMITTEE, SAN FRANCISCO, CA

Dr. BEARY. Thank you very much, Senator Weicker.

The magnitude of this disease has been well laid out, and I will not dwell further on that in view of our time constraints.

I will make a point that finding anti-viral drugs is a very difficult thing to do. One of the exhibits in my written statement shows that, despite intense research activity since 1945 in this country, only seven anti-virals have been developed compared to a couple of hundred anti-bacterial drugs. So it is a difficult area of biology.

Another point I will make in response to interest by the staff has to do with the treatment IND issue. To summarize this, I think one could say that circumstances have changed. These procedures may have been useful at a time when a smaller number of people were affected by AIDS. But we are in a situation now where there are a million to 1.5 million people infected with the virus. It is difficult to see how the primary care doctors, whom we have heard all the witnesses say are going to be very much involved in the care of AIDS patients, are going to be able to cope with complex procedures to obtain medications. Phone calls to obtain the drug, filling out forms, consulting an institutional review board, formal informed consent are necessary. This is in the context of a busy practice where the beeper is going off and there is one patient on the phone and one sitting in front of you and three or four outside the door waiting to come in. It is just hard, having been in the primary care arena myself, seeing how those procedures will work for a disease affecting large numbers of people. So my written statement addresses some of those concerns.

Distribution problems deserve comment. My statement makes the point that when you have enough evidence of effectiveness for a treatment IND, experts in our companies feel that you should be close to approving the NDA itself. My point is that when an NDA is approved, you can get the new medicine in any pharmacy in the city with just a prescription. You do not have to go through all

those logistical procedures previously mentioned. So we should not lose sight of the fact that once regulatory action is taken many things are still needed to get new medicines to patients. Large scale manufacturing and distribution must proceed so these medicines are available in a convenient way to primary care doctors, who are, as you know, the base of the medical care pyramid.

In regard to the NIH AIDS clinical trial group issue, one of the charts you have in my written testimony makes it clear that discovering and developing drugs is a very complicated process. There are lots of things going on in parallel and serial, and so one must use tools from the discipline of project management, techniques that one uses to set off a space shot or to build a skyscraper. There is a management dimension to all of this as well as a scientific dimension. And we should not lose sight of that. In fact, probably half the things we have been talking about today are management issues—personnel, project management, matching demand to capacity (aggregate planning) et cetera.

Our R&D directors would be happy to meet with Dr. Fauci to contribute whatever we can to their efforts. And I would be happy to facilitate such a meeting if they would find it useful.

I will move to a conclusion by saying that 46 firms presently have 50 AIDS-related drugs and vaccines under development. We have to remember the odds are that most of them will not make it all the way through to the pharmacy. That is the nature of drug discovery. But we do have a major commitment to searching for answers for this alarming disease.

Mr. Chairman, that is a quick summary of my major points. I would be happy to respond to questions.

[The prepared statement of Dr. Beary follows:]

DRAFT Draft / 11 July

Statement of

John F. Beary, M.D., M.B.A.

U.S. Senate

Committee on Labor and Human Resources

July 13, 1988 / 9:15 a.m.
Dirksen Blg. / Room 430

Mr. Chairman and Members of the Committee:

I am Doctor John F. Beary, Senior Vice President for Science and Technology of the Pharmaceutical Manufacturers Association. I am board certified in internal medicine and rheumatology and hold an M.B.A. degree. PMA represents the more than 100 research-based pharmaceutical companies that discover, develop, and produce most of the prescription drugs used in the United States. Last year, PMA firms spent 5.4 billion dollars on medical research and development.

The Challenge of Developing AIDS Therapies

The scope of the AIDS epidemic has alarmed and mobilized the nation. CDC estimates that about 1 million Americans are infected with the AIDS virus. Since June 1981, 62,500 cases have been reported and 56% of these patients are dead. This fearsome disease is affecting the lives of all Americans as we care for those who have it, promote prevention programs, and search for safe and effective treatments.

AIDS is one of the most difficult problems ever faced by the medical profession for two reasons. First, AIDS is a viral

disease. Secondly, the mechanism by which HIV (Human Immunodeficiency Virus) causes disease is unusual and makes discovering a treatment even more difficult.

Although the pharmaceutical industry has had great success in discovering and developing hundreds of antibacterial drugs over the past 50 years, only 7 antiviral drugs have been developed during this time [Figure 1]. The reason is that antibacterial drugs interfere with biochemical processes unique to bacteria and do not harm the human host.

In contrast, viruses are intracellular parasites that use normal human processes for their own survival. Thus medicines that destroy a virus often cause unacceptable toxicity to the human host because the medicine may destroy the patient's own cells as well.

Even though we have learned a great deal about the biology of rabies virus, influenza virus, and coxsackie virus during the past 50 years, we still do not have curative treatments for established rabies, colds, or viral meningitis.

The second reason that AIDS is such a research challenge has to do with the mechanism by which the virus causes disease. The HI virus implants its genes into the patient's own chromosomes at the time of infection thus resulting in lifelong infection. We do not presently have a technology for eliminating the cells that are diseased, nor does one appear to be on the immediate horizon.

Therefore current efforts are focused on secondary issues such as suppression of viral replication and prevention of damage

to the immune system and central nervous system. Treatments for the complicating infections of AIDS are also receiving research emphasis.

The AIDS crisis thus raises two important questions that I will address: (1) What is being done to discover new treatments and (2) Are there barriers that prevent an effective new treatment from arriving quickly at community pharmacies?

Drug Discovery and Development Process

It takes about 10 years and costs an average of $125 million to take a new medicine from the laboratory bench into the pharmacy. An average of four thousand test compounds must be evaluated to yield one compound that is available for the doctor to prescribe [Figure 2: funnel].

The steps in the drug discovery and development process are:

1. Compound Discovery: During the basic research phase, synthesis of a compound and identification of biologic activity take place.
2. Animal Testing: Therapeutic and toxic effects are identified.
3. Human Testing: An IND (Investigational New Drug) application is filed with the FDA.
    - o Phase I assesses safety data in about 50 normal, healthy volunteers and takes approximately 1 year.
    - o Phase II is a pilot efficacy study involving about

200 patients and takes 2 years.

o Phase III consists of more extensive controlled clinical trials involving 2,000 to 4,000 patients and seeks to confirm the efficacy data and to look for adverse reactions. These trials last about 3 years.

4. NDA (New Drug Application) Review by FDA. NDA Approval.

5. Full scale Manufacturing and Distribution.

Figure 3 summarizes this information. [Timeline].

Treatment IND Issue

In our opinion, Dr. Frank Young and his staff at FDA have made approving AIDS related drugs a high priority and have worked hard at this task. The PMA has consistently offered testimony supporting appropriations to give FDA the personnel and facilities needed to cope with their heavy workload.

The revised Treatment IND rule became effective in June 1987 as a result of FDA's well-intentioned desire to get drugs to desperately ill patients faster. It was hoped that setting up a new system outside the normal drug approval, manufacturing and distribution system would help with the problem. However, as the number of people afflicted with AIDS increases, it appears as if this system will not be able to cope with the increasing demand for new medicines. Perhaps it is time to re-examine the Treatment IND policy in the light of these new circumstances.

Our member firms have raised the following concerns about the Treatment IND program:

1. Problems Proving Effectiveness. The program could well lead to decreased enrollment in clinical trials. If patients can get a promising medicine through the Treatment IND program, why would they enter a controlled trial and take a chance on getting a placebo or a control drug?

A situation is thus set up whereby the sponsor company is left in limbo and unable to complete the clinical studies needed to approve its NDA because of an insufficient number of patients enrolling in the trials. Data collected outside the clinical trial mechanism are not acceptable to the FDA.

The Treatment IND rule also leaves some uncertainty about the quality of evidence that must be presented to qualify for a Treatment IND. The Federal Register discussion contains terms such as "sufficient information" and "sufficient data" which are subjective and open to wide interpretation.

2. Logistic Issues. Logistical problems may also inhibit the success of the Treatment IND program. When an NDA is approved, full-scale drug manufacturing, physician education and distribution activities take place that put the new medicine in every local pharmacy that wishes to stock it. These activities do not take place under the Treatment IND program. Physicians wishing to use an IND drug must make phone calls to obtain the drug, fill out forms, consult an IRB (Institutional Review Board), and obtain a formal informed consent from the patient. These procedures might suffice for a disease affecting a small number of people. However the cumbersome logistics necessary for

a drug of unproven effectiveness or safety suggest that the Treatment IND program will have a hard time coping with the one million people infected with the AIDS virus.

3. Liability Issues. The liability issue affects both pharmaceutical firms and physicians. At a time when American courts are already jammed with lawsuits, our companies have grave concerns about providing drugs of unproven safety and effectiveness to the public. Primary care physicians, who are essential to providing care for AIDS patients, also face major medicolegal threats in their practice environments. This factor will likely chill a doctor's willingness to use an experimental drug in the office setting.

In conclusion, the Treatment IND program must not be seen as a substitute for full NDA approval of a new medicine. It's purpose is to serve as an interim, emergency measure. As I mentioned, full approval sets into motion important manufacturing and distribution actions which make a new medicine widely available to physicians and their patients.

NIH AIDS Clinical Trial Group Issue

NIH has played a valuable role as facilitator of drug development activities among industry, academia, and government via the National Cooperative Drug Discovery Groups program. By serving as a matchmaker, NIH has brought together organizations that have complementary capabilities that can advance drug development.

The NIAID (National Institute of Allergy and Infectious Diseases) established the AIDS Clinical Trial Group in 1986 and has set up a network of 35 ACTUs (AIDS Clinical Trial Units) to develop AIDS therapies. This is indeed an ambitious undertaking and a great management challenge. Over the past 50 years, our companies have found that project management expertise is a key discipline necessary to accomplish efficient and effective drug development [Figure 4]. A large number of important activities must proceed in parallel fashion. Keeping this network of drug development steps coordinated requires the sophisticated management techniques that make possible construction of a skyscraper or the successful launch of a spacecraft.

Pharmaceutical Industry Effort

Forty six PMA firms have 50 AIDS related drugs and vaccines under development [Figure 5- AIDS product chart 5/88]. These products include 16 anti-virals, 21 immunomodulators, 3 anti-infectives, and 10 vaccines. In addition, 10 diagnostics have been approved and 23 others are under development. Although the odds are such that most of the therapeutic products will not make it all the way through the drug development process, the number of products under development emphasizes that the pharmaceutical industry has made a major commitment to search for answers to this alarming disease.

PMA is one of the financial supporters of the Institute of Medicine (IOM) Roundtable for the Development of Drugs and

Vaccines against AIDS. IOM will appoint a steering committee of experts from academia, the pharmaceutical industry, the federal government, and the public. The aim of the Roundtable is to monitor the state of the science, discuss policy issues, and identify opportunities to expedite drug and vaccine development.

Conclusion

We face a formidable challenge as we assemble the basic science information necessary for therapeutic advance. The research-based pharmaceutical industry understands the urgency of discovering and developing drugs to combat AIDS, and has mounted intensive efforts to that end.

Thank you.

Figures

Fig 1: Antiviral drug list

Fig 2: R&D Funnel

Fig 3: Drug Development Timeline

Fig 4: Project Management

Fig 5: PMA AIDS chart

Senator WEICKER. Why don't we move to the other members. Thank you very much, Dr. Beary. Why don't we move to Dr. Gingell?

Dr. GINGELL. Thank you, Senator Weicker, for providing an opportunity for me to share my view of the Nation's overall effort to find effective treatments for AIDS and HIV-related illness.

I am a physician specializing in internal medicine and was trained at NYU Medical Center and Bellevue Hospital. Currently, I serve as director of Medical Information of the Gay Men's Health Crisis, a non-profit, voluntary agency devoted to addressing the grave problems arising from the HIV epidemic. In addition, I am a member of the Institutional Review Board of the Community Research Initiative in New York, one of the groups that were mentioned in prior testimony.

I am afraid my assessment of progress at the Federal level on AIDS drug development and approval is quite different than the picture painted by Dr. Fauci and Dr. Young. Repeatedly, in public testimony and statements to the press, we have heard that every possible action that could be taken to identify and evaluate potential treatments for this devastating virus has been taken.

Consistently, the public message has been "AIDS is our number one health priority and we are pulling out all the stops to fight it." Tragically, that is not what the record shows has been happening.

From where I sit, the Federal AIDS drug development program is better described like this: A brand new Government bureaucracy with an annual budget approaching $150 million that has: one, put most of its eggs in one basket—that is, AZT; two, spent two years reinventing certain systems that exist in abundance in the private sector; and, three, exerted most of its energy endlessly scrutinizing new ideas instead of rapidly investing resources in those ideas to get desperately needed answers.

Let me make it clear at the outset that I am not an advocate of any particular drug or agent. What I do advocate is an overall approach to AIDS drug evaluation that is consistent with the urgency of the epidemic. What exactly does that mean?

In the face of a public health emergency, it means re-evaluating the risk/benefit tradeoffs that we are prepared to accept in testing potentially promising drugs. It means re-evaluating the clinical trial "endpoints" or criteria that are used to judge whether a given drug can be deemed effective, or "promising." And mostly important, it means the overseers of the Federal drug development effort must develop a more open-minded stance toward candidate anti-AIDS agents.

The fact is we are not dealing with a field of shimmering white horses in the race to come up with treatments for AIDS. We are stuck with dark horses of different shades running against very long odds. But if there is even a chance that a candidate AIDS therapy could be useful—that it might buy a few months of extra life for certain patients with AIDS—we cannot afford to ignore it.

Let me take a minute, Senator Weicker, to just reinforce the need for drugs other than AZT. A person who is given AZT today one year later can expect a 40 percent chance of a serious toxic effect, and has a 25 percent chance of having to go off the drug en-

tirely. We, therefore, desperately need other therapies than AZT for this disease.

It is easy and certainly safer for a Federal program manager or a duly appointed panel of experts to warn that Drug X probably will not be the long-term solution to the HIV dilemma. But these a priori kinds of conclusions do not get the work done or give us the essential data that is needed to decide which drugs to scrap and which to aggressively pursue.

The whole point of assembling this enormous network of medical institutions called the AIDS clinical trial group is to be able to get a well-designed clinical trial up and rolling rapidly, to have qualified investigators at multiple centers working to find answers on toxicity and efficacy on as many promising agents as possible. Unfortunately, to date, that just is not happening.

Case in point, dextran sulfate, a drug which last November the NIH's clinical drug development committee rated "high priority," and that ten different laboratories have found have anti-HIV activity in the test tube. In additional, dextran sulfate has been used for over 20 years in Japan for the treatment of other diseases, so we are not talking about an unknown agent.

Facing a global health emergency, one would expect that dextran sulfate would have immediately moved into a small scale pilot study within the NIH system. Instead, eight months later, not one patient has received dextran sulfate in a federally sponsored study.

The problem is certainly not a lack of clinical study volunteers. Literally thousands of desperate Americans who cannot tolerate AZT and have no other treatment options would gladly participate in a compassionately designed trial of dextran sulfate.

Where, then, did the dextran sulfate express get sidetracked? In December 1987, we are told that a protocol concept proposal was submitted by a top clinical investigator who was already conducting a small company-financed trial of dextran sulfate. What happened to that submission? Somehow it got lost in the NIH's AIDS program's electronic mail system. By March 1988, dextran sulfate was on the agenda for the AIDS clinical trial group meeting, but there were concerns raised, principally about absorption of the drug into the bloodstream.

What did the Federal AIDS program do to actively address these concerns and solve the problem? Essentially nothing, except to tell a tiny pharmaceutical company on the other side of the world to do the essential pharmacological work and report back to NIH. Mercifully, Waynofan Chemicals of Japan managed to furnish enough data last week to allow the first NIH study to go forward.

I wish I could report to you that dextran sulfate is an isolated example within NIH. It is not. There are easily ten agents selected for clinical study by NIH's own drug committee, assigned a high priority, and caught up in bureaucratic red tape, and which have yet to enter human study in the Federal AIDS program. We are not talking about quack remedies or snake oils. We are talking about agents that preliminary studies suggest might be useful in AIDS.

How could these delays occur in the face of a public health disaster such as AIDS? Let us first dispose of the few of the most familiar excuses:

"We must do nothing that could harm patients . . . These things just take time." In fact, there has not been a drug in history that did not entail a margin of risk to early recipients. Calculating what is an "acceptable" margin of risk depends on the threat posed by the illness. Believe me, we are a long way from the point at which our experimental treatment efforts in AIDS, taken as a whole, could be said to constitute a greater hazard to HIV-infected people than HIV itself.

Well-worn excuse No. 2: "It is better to focus our energies on the few drugs that are really promising." How do we find out what is actually promising without doing studies? Unfortunately, there is no good animal model for AIDS, and the only reliable test of what works must be carried out in people.

Senators, we have not even started the work that must be done to find out which of many candidate therapies is most promising. Apart from a few studies to gain a better understanding of AZT, Dr. Fauci himself seems to be telling us that the NIH AIDS drug program has spent most of the last two years getting staffed and organized. It is time to set some hard and fast goals for the clinical testing machinery that Congress and the taxpayers have paid to create.

Which brings me to the last of the familiar excuses: "We only have so much money and cannot pursue every drug that comes along." I do not know what more the U.S. Congress can do to demonstrate its willingness to spend what is needed to put the AIDS nightmare behind us. When the AZT breakthrough came in September 1986, the U.S. Senate was certainly there with $47 million in needed extra funds.

The time is overdue that the Federal clinical testing program abandon its "wait and see" attitude and start using its resources to "go and do." If there are problems blocking an important trial, the NIH Aids program must get to work to solve them.

With your permission, Senator, I would like to just take a couple of minutes to make a final observation about the Food and Drug Administration, specifically in regards to the treatment IND issue.

A year ago, with great fanfare, the FDA announced the adoption of a new rule concerning treatment IND's. According to Commissioner Young, the change in FDA regulations would mean accelerated release of promising experimental treatments to people with life-threatening diseases, such as AIDS.

I believe it may have been Commissioner Young's intention to make a well-meaning gesture that would give hope to people facing this devastating disease. But what the FDA has actually given us is smoke and mirrors—a rule that says one thing with a totally different standard being applied in actual practice.

Let me remind you that the exact wording of the treatment IND regulations are that drugs which "may be effective" and that are safe would be candidate drugs.

Large drug companies want nothing to do with the treatment IND, and small ones that might consider it are being advised not even to apply unless they have done all the work to prove true efficacy—except for crossing t's and dotting i's.

It is no mystery that there are not a number of treatment IND applications under submission, because the operating standards at the FDA are effectively the same.

As both a physician and a person who has AIDS himself, let me say for the record that the FDA's well-meaning gesture has backfired. If it has done anything, it has falsely and cruelly raised the hopes of people with AIDS. Facing AIDS is tough enough. It is no act of kindness to tell us that help is on the way when the reality is that nothing has changed at all.

Thank you.

Senator STAFFORD [presiding]. Thank you, Dr. Gingell. Dr. Conant, we would like to hear from you.

Dr. CONANT. Senator Stafford, thank you so much for allowing me to address you this morning.

I returned from the Fourth International AIDS meeting in Stockholm last month, absolutely convinced that we are not doing enough to provide drugs for the 1 to 2 million Americans that have been affected with the AIDS virus.

Perhaps one of the things that I can do this morning, as a practicing physician, who has diagnosed between 800 and 1,000 cases of AIDS in my practice in San Francisco, is to bring back to the committee some of the human dimension of this disease.

You know, often we think that someone contracts AIDS and then dies, and the period of time between diagnosis and death is usually overlooked by the community, not having to deal with this problem on a day-by-day basis. It is during that time that I actually see the patient, and it is during that time that I hopefully can provide drugs to prolong his life or reduce his pain.

Most of the patients I see are healthy at the time they get AIDS, because they develop Kaposi's sarcoma, this unusual malignancy of the skin.

The patient is usually jogging 5 to 8 miles a day; he is usually working out at the gym two or three times a week, because he is afraid that he is been infected with the AIDS virus. And then one day while dressing he looks down at his thigh and he sees this purple bump, and he knows that indeed he is got Kaposi's sarcoma, and he comes in and we take a biopsy, and he waits a week to find out what it really is. He knows, and I know, and you know. But he waits through that limbo of a week to find out is he going to be dead in 5 years, or not.

And he comes in, and we tell him he has AIDS. And then slowly, inexorably, over the next 2 or 3 years, that young man has to watch himself daily, in the mirror, lose weight, become ashen, turn gray. He sees that body that was young, and virile, and handsome just a year ago, now become a shell.

Look down and see that he is covered with these purple tumors. If he is lucky, he will die of one of the opportunistic infections, because he will die in a few weeks. He may get pneumocystis, which is like smothering to death.

He first becomes short of breath, breathing becomes more labored, he cannot get his breath, and he suffocates. But it's fast. If he is unlucky, he may die of Kaposi's sarcoma.

It is not a merciful death because the malignancy does not involve the brain and so the man is conscious until the moment of his death.

One of the health-care providers that worked with us developed a lesion in his throat, and so as he was sitting on his death bed, looking at himself in the mirror of his bedroom, covered, now, with this tumor, this hideous figure of a previously handsome man, he had to sit bolt upright in bed because every time he laid down he would choke on this tumor in his throat. And he sat there until he died.

On Monday of this week, I saw a patient who I had started on AZT back in January because his health was failing, he had fatigue, he could no longer work. This is a 28-year-old boy. I also started him on pentamidine by inhalation to prevent pneumocystis, a procedure that has not yet been approved by the FDA but is in wide use in the community because we can substantially prolong the lives of people infected with this virus.

On Monday he came in showing me two purple lesions, one on his back and one on his leg, and we biopsied them. Now we know what they are, and he knows what they are, and when he comes next week I must tell him that he has got Kaposi's sarcoma.

And the first question he is going to ask me is what are we going to do? I am already receiving the only two treatments that are known to treat this disease.

Now, we train our young people to be brave and heroic, and courageous. A man wounded on the field of battle is supposed to get up and keep fighting. That is what we have selected for in this community.

Now this man is going to get up and he is going to keep fighting. He is going to fight for his life against this invader which has invaded his body.

And he is turning to me for the tools to wage that battle, and I have not any tools to give him. And so from our perspective, we want to see the FDA, and the National Institutes of Health, and academia, move as quickly as possible to give us drugs which may not cure this disease, but at least can prolong these people's lives and give them some hope.

We heard from Dr. Young this morning, that we may have cut 2 or 3 years off the process, and we may in fact be able to get a drug in 5 years. The patient that I am describing knows that he will not be here 5 years from now. None of the patients that I am currently seeing will be here 5 years from now.

In California, we perceive that the FDA is in fact moving too slowly. Now we do not blame Dr. Young. Dr. Young, without the proper leadership from the White House, cannot subvert the mandate of his agency.

We are going to have to give him the authority to make the regulatory changes that you heard referred to this morning.

But in California, we have enacted legislation to allow us to test drugs through our own State Department of Health, Food and Drug Administration.

Within a week of passing that legislation last September, Jonas Salk submitted a proposal, it was approved within a month, he had it in humans by November, and he had data to report to the meeting in Stockholm.

The procedure can be expedited and we have demonstrated, in California, ways in which it can be accomplished.

The other perception that I had in Stockholm is the fact that community-developed drugs are not getting the priority that designer drugs are receiving, and you heard that alluded to earlier this morning.

Let me try to make that understandable. Physicians, for centuries, have observed that certain drugs given to certain patients have amazing results.

In 1936, it was observed that if you had a patient with this rare disease, dermatitis or pediformis, and you gave them a sulfone, the dermatitis or pediformis went away.

We still, 52 years later, have no idea why that drug works, but it does. DH is not an infectious disease, and were you to come to my office today, I would give you a sulfone to treat dermatitis or pediformis.

Now the other way of developing drugs is to actually look at what's needed, and design a drug to accomplish that. Burroughs-Wellcome did that. They designed acyclovir to block the replication of the herpes virus, a designer drug, the acme of science. That is what we want scientists to do.

And so a great deal of the funding should appropriately be designated for designer drugs which will go through the process and be available in the next 5 to 15 years to give us treatments that we do not currently have.

But my patients are asking: are there any of these drugs—AL-721, naltrexone, dextran sulfate—which have been purported in the community to have efficacy—are there any of these drugs that will prolong my life, decrease my chance of dying?

These are the studies that we feel are urgently needed and must be accomplished quickly by the NIH, and the FDA, and others receiving grants.

Now there are two reasons why these things are not moving ahead quickly. The first is leadership. You have heard over and over today, and we have the same perception in California—the Administration has not provided the necessary leadership to respond to this problem.

And the other is that Federal officials cannot be candid when they come up here to report to the Senate and the American people.

For those of you who are interested, there is an excellent review of that in Science Magazine August 21st of last year, 1987, pointing out that when Dr. Wyngaarden came for the entire budget of the National Institutes of Health, he had originally requested $6.9 billion. The Office of Management and Budget told him that he could ask for $5.2 billion.

And then he had to come up here, and Congress had to beg him to accept another $1.5 billion, and he had to reluctantly sit there and acquiesce against all of this pressure from Congress to take the money that he knew he needed to run his agency.

And Dr. Fauci has told us, repeatedly, that everything is being done, and then we learned in April that in fact studies were not going forward because he did not have the manpower.

Now when scientists come before us, men whom we respect, men whose judgment we respect, men whose veracity we respect, and are having to bring before us Reagan New Federalism in the guise of science, we do not know when the trust ends and the New Federalism begins.

And so one of the problems is that we do not know what to believe at this point.

Now, some of these problems can be quickly addressed. Some of the things that have been done in California to speed up drug review we would commend to the FDA.

In the Presidential Commission's report they called for 50 new FTEs at the Food and Drug Administration to speed up the review process. We would endorse that, as we do all of these recommendations, which are excellent.

Finally, I was reminded, in reading the commission report last week, that it occurred only with the urging of Congress. The Administration had been reticent to set up this type of commission, even though many of us had been advocating it for the past 7 years.

We hope that the President will move quickly to implement these recommendations. If he does not, then Congress may well have to assume the mandate of legislating these recommendations, to bring these recommendations to the American people in a timely fashion.

Thank you, Senator.

[The prepared statement of Dr. Conant follows:]

STATEMENT Before the Committee on Labor and Human Resources

Hearing on AIDS Treatment Research and Approval

Marcus A. Conant, M.D.
Chairman, AIDS Leadership Committee
California State Department of Health

Wednesday, July 13th, 1988
SD 430

Senator Kennedy and esteemed members of the Labor and Human Resources Committee:

I returned from the Fourth International AIDS Conference in Stockholm last month convinced more than ever that we are not doing as much as we need to to provide treatment for the hundreds of thousands of Americans who have been infected with the AIDS virus. This morning, I would like to outline briefly for you four policy areas where I think we have failed, and to recommend to you specific solutions for those failures. Before I begin, let me tell you a little bit about who I am, and the perspective from which I speak.

I began caring for patients with sexually transmitted viral diseases at the Haight-Ashbury Free Clinic during my residency at the University of California Medical Center in 1964, when the genital herpes epidemic was just beginning, and for the last twenty years I have devoted a great deal of my academic time to scientific investigation into this and other diseases. Beginning in 1981, the new sexually transmitted disease AIDS began to consume more and more of my time and energies. I started the first AIDS clinic in the United States at the University of

California in the summer of 1981, where I was quickly joined by Drs. Volberding and Abrams. That clinic has grown to be the renowned AIDS Clinic at San Francisco General Hospital. I was instrumental in starting the organization which gave birth to the San Francisco AIDS Foundation. Last year, I helped California Attorney General John Van de Kamp draft the bill which allows us to test drugs in California under our own state Food and Drug Administration division of the Department of Health Sciences. Finally, I currently serve as the co-chair of the state Department of Health AIDS Leadership Committee, which is charged with overseeing the public health response to the AIDS epidemic in California.

Often, when I speak to groups of policymakers, I find that don't understand the viewpoint that I bring as a practicing physician to this problem. And so, with your indulgence, let me take a moment to tell you what it's like to watch a young man be diagnosed and die of this disease. Too often, we think that someone gets AIDS and then dies quickly, and we don't focus on that period of time between developing the disease and death. It is during this period of time when I interact with patient, when I can watch the patient's response, and of course, when I can offer treatments to prolong the patient's life and decrease his suffering.

Imagine, if you will, being 32 years old, in the prime of

may die of the malignancy Kaposi's sarcoma. It is a slow death, one that disfigures but, cruelly, invades every part of your body but your brain, so that you are fully aware of your frightening appearance and your slow progress towards death. For instance, one of the healthcare providers who worked with me at the Kaposi's sarcoma clinic at UC and developed Kaposi's sarcoma, developed a large lesion in his throat so large that he could not lie down because it would choke him. and so had to sit bolt upright in bed, gasping for breath around this mass in the back of his throat, while he slowly, slowly died.

On Monday, I saw a patient whose health had been failing since the first of the year. His white count had been dropping, his helper T-cell count had been declining, and he was becoming more and more fatigued. We had started him on AZT, we had started him on pentamidine, and he was receiving all of the drugs that we have available to treat this disease--and on Monday, the day before yesterday, he walked into my office with lesions on his body that had developed this weekend. Purple nodules. I had biopsied them and we were waiting for the results. I know what they are. He knows what they are. You know what they are. Now, when he returns next week and we begin to chart what we are going to do, it will already have occurred to him that he is doing everything that is known to do. He is taking the one drug that is known to help, AZT, and he developed Kaposi's sarcoma while on it. We have already done everything that we can do, and yet his

disease is progressing.

What should not surprise anybody in this room is that that young man will continue to fight for his life. All of us are the product of natural selection. Many of us have been taught that when wounded on the field of battle, you get up and keep fighting. You don't sustain a wound and lie down and die. This man has been wounded from within by an invading virus. He is going to get up and keep fighting for his life until it kills him. You and I would be disappointed in him and in his fighting spirit if were he to do less. And yet when he comes to me for weapons to fight this invader, I have to turn him away.

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Let me now discuss the four policy areas where I feel that we can demonstrably move faster.

I. The Food and Drug Administration (FDA) must move faster to solicit new drug applications and to approve new investigational drug requests. While it is true that AZT was approved rapidly (3-1/2 months, I believe), at a cost of $600,000, you must keep in mind company that has the greatest experience in developing antiviral chemotherapy. And you must also keep in mind that it is very fortunate that AZT has worked as well and as quickly as it does. Unfortunately, smaller companies without the resources

or expertise of Burroughs Wellcome are having far greater difficulty shepherding their experimental drugs through the labyrinthine processes of the FDA. Last year in California, we passed legislation which allows us to review and approve for testing new investigational drug applications within California. To date we have done an exemplary job. We have maintained the same high standards of review that the FDA has developed over the last 20 years while expediting the process simply by committing ourselves to do everything possible to get the studies to the reviewers and through the approval process as quickly as possible. As a clear example that this is working, drugs that were submitted in parallel to the California and the federal systems are being approved by the California FDA sooner than by the federal FDA.

II. The second major area of concern--and this was highlighted in Stockholm--was the disparity between research on community-developed drugs and that upon what I will call "designer" drugs. Let me explain to you the distinction I am trying to make between these two terms. In medicine, it has been observed for centuries that sometimes a drug comes along; no one knows how it works or what it does, but when given to a diseased patient, often by pure serendipity, the patient improves. This has already happened with AIDS: AZT makes the skin disease psoriasis improve dramatically. No one expected this. We had no reason to believe it. No one thought that psoriasis was a retroviral disease, and

we still don't know if it is. But AZT makes psoriasis better. I am currently studying this very issue. In 1936, when sulfonamides became available, it was observed that a very rare condition, dermatitis pediformis, which as far as we know is not an infectious disease, was dramatically improved when patients were given a sulfa drug. For the last 52 years, this association has been studied, and to date we have no explanation for why sulfonamides cause improvement in dermatitis pediformis. Nevertheless they do, they have been approved by the FDA for this use, and if you see me today in my practice I would give you this drug, which was discovered in the community to have efficacy, for your condition.

The flip side of the community drug is the designer drug. A beautiful example is acyclovir. A few years ago, the Burroughs Wellcome Corporation made a commitment to find a drug that would treat a viral disease. They sat down and they tried to design a drug which would block the replication of the herpes virus. They were successful in doing that, and today we have acyclovir, which specifically prevents the replication of the herpes virus. This is science at its best. The drug is safe and effective, it is in wide use and it does the job for which it was intended. It was carefully studied by the FDA. I entirely endorse the process that they put it through to be sure that it was safe; they were going to give it to hundreds of millions of young, sexually active people who were going to produce our country's next generation, and we wanted to be absolutely certain that it was

safe. I have no qualms with the way that the FDA reviewed this drug.

But what we found at the International AIDS Conference in Stockholm is that most of the research funds in the United States, for which 300 million dollars have now been appropriated, are going to designer drug research at the National Institutes of Health (NIH), academic centers, and elsewhere. Very little of this money is going to study community-developed drugs. It is perfectly appropriate that the lion's share of research funds go to designer drugs, because we all acknowledge that, eventually, that is where the heavy-duty drugs that will one day conquer this disease are going to come from. But the process of designing, developing, and testing the drug, getting it to human subjects, and (finally) developing it for the market is a process of many years--at least five, perhaps ten or more. The man who I am treating today, the man who is coming to me for me to tell him that he has Kaposi's sarcoma next week--he knows that he is not going to be here five years from now. He can't wait for those designer drugs to be developed. I went to Stockholm hoping to hear data about some of the drugs touted as possibly efficacious --AL 721, naltrexone, dextran sulfate--and many of us went from poster to poster, trying to find drugs to use for our patients. And what did we find? We found that often the studies for these drugs have not even been approved, that the studies are not being done, that the funds which Congress is appropriating in the name of the American people are not being used to test those drugs

which are purported to have some efficacy in restoring the immune systems of AIDS patients and keeping them alive.

III. The third major of concern is the fact that we do not have an animal model to study this disease. The only animal that can be infected with the AIDS virus and become ill is man. We learned in Stockholm that a close relative of the AIDS virus, HIV-II, infects macaques (such as rhesus monkeys), and that some of these monkeys develop opportunistic infections. This is the first rumor that there may be animal models available to study AIDS. We can move faster in our animal studies than in human studies. I would give an animal higher doses of an experimental drug than I would give my own son. Congress needs to hear this and to understand that we need to appropriate funds for expanding animal-model facilities to search for drugs that are effective both as vaccines and as treatments.

IV. Finally, and unfortunately, we heard over and over in Stockholm that the traditional approaches are not working. This virus is going to be tougher than most of us even feared. Attempts by Dr. Salk and others to develop vaccines are not working; the vaccines are not effective. AZT prolongs the lives of patients and reduces the recurrence of opportunistic infections, but unfortunately the virus mutates and eventually becomes resistant to AZT. This means that we need to return to basics. This means that we have to invest even more funds into

basic virology, basic immunology, and basic pharmacology to understand how this virus produces disease in humans. And the parallel is easy to understand: you infect a human with this virus, he seroconverts and becomes infected, and the virus begins to destroy his helper T-cells relentlessly. You infect a chimpanzee with this virus, and the chimp becomes infected, but his helper T-cells remain normal. The virus seems incapable of destroying the chimpanzee's helper T-cells. What's the difference? How are we, as you humans, different from chimpanzees? If we could answer this one question, we could understand how this virus is capable of killing us and not killing our closest animal relative. Ultimately, what all of this tell us is that we must go back to basics to invest larger amounts of money into basic science to understand and unravel the pathophysiology of this disease.

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What are some solutions to these problems? First, let me point out that we have two generic problems with this epidemic, and indeed with many scientific problems with which our government is trying to grapple. The first is a lack of leadership. From the beginning, I and others have come before Congress and pleaded for funds, we tried to point out the seriousness of the problem, and Congress has responded by appropriating funds to help with us prevention efforts, with

education efforts, and with treatment efforts. Unfortunately, those funds have not been used appropriately. There has been inappropriate leadership from the White House, and virtually no management of the epidemic. We can keep pouring funds into AIDS research, and those funds can be sent to the CDC, or the NIH, but someone needs to sit down and prioritize exactly how those funds should be spent. These moneys should be spent for community-developed drugs, and this amount of money should be spent for designer drugs; this much should be spent for basic virology, and this to develop treatment for AIDS-associated conditions; and these will be the steps to expedite those studies. This kind of leadership, this kind of management, and this kind of basic coordination has been lacking during the first seven years of this epidemic--during Mr. Reagan's administration.

The second generic problem is the fact that scientists, working for the administration, have difficulty in being candid with Congress and the American people. This a terrible problem which only confuses Americans, confuses Congress, and worries all of us. There was an excellent article in the esteemed magazine Science, in August 1981 (87?), pointing out that Dr. James Wyngaarden, the director of the NIH, developed a budget to run his institute for 1988, and that budget was 6.9 billion dollars. He submitted it to the President, who had it reviewed by the Department of Health and Human Services and by the Office of Management and Budget. They slashed his budget down to 5 billion dollars, almost 2 billion dollars less. Dr. Wyngaarden then had

to come to Congress and, in hearings before the Appropriations Committee, he had to insist that he could run his institute with $2 billion less than he knew he actually needed. And he had to sit there while Congress forced him to accept moneys which he was not asking for but knew he needed. Now, the mendacity of this kind of machinations boggle the mind. You begin to wonder, Can we believe the Dr. Wyngaarden when he tells us that things are facts? when he tells us that the NIH is doing everything it c[illegible] to attack AIDS? Is he giving us his scientific opinion, or is he espousing Reagan's New Federalism? You may think that I have picked an isolated example, but you will recall that in April Dr. Fauci came to the Hill to testify before Representative Weiss' subcommittee. Dr. Fauci has held and stated publicly on numerous occasions that everything is being done to move AIDS drug testing along as quickly as possible, and that the impediment is the fact that there are no drugs out there, and not the fact that there are deterrents within his agency. Under questioning from Representative Weiss, Dr. Fauci admitted (and here it is in the New York Times) that there are delays in his agency because he lacks the personnel to do the job. It is my understanding that, since those hearings, he's been allowed to hire 30 additional people. It is shameful that the scientific leaders of our country cannot come to Congress and be frank and candid in replying to direct questions relating to the health of our citizens.

As far as specific recommendations which address the

problems I have been discussing, I would first mention that the recommendations of the Presidential Commission on HIV Infection embody specific recommendations which address all of these problems. I have reviewed these recommendations, and I endorse them completely. The work has been done by Admiral Watkins and his commission, and it has been presented to the President; we now must demand that these recommendations be implemented. The FDA needs to speed up new drug applications; I would particularly remind you that the Presidential commission recommended 50 new FTE positions to accomplish that end. The FDA should look to the California model of drug review to understand how the process can be speeded up significantly. And finally, the FDA needs to monitor its internal procedures to be certain that AIDS drug applications are being moved through as quickly as possible, and that they are not delaying the review of other traditional drugs. I am mindful of the fact that, just recently, as Dr. Young mentioned, the Food and Drug Administration has taken steps to alter their internal structure by developing a Division of Antiviral Drugs. I would suggest that it needs to monitored extremely closely, to see that it is accomplishing the necessary end, and if in fact other AIDS-related drugs which are **not** antiviral--immune stimulators, for instance--are bogging down the FDA review process, an entire AIDS Division to review AIDS-associated drugs exclusively may need to be created. Unfortunately, more money is going to be needed. We are going to have to appropriate moneys for development of animal models for

this disease. This disease is going to be with us for the rest of our lives, and our children's lives, and unfortunately, their children's lives. We need to move as quickly as possible to develop new drugs, new treatments, and new scientific understanding, and we're going to have to use animal models to achieve this end. Funds for these animal model resources are going to be desperately needed. We also have to return to basics. We are going to need increased funding for basic virology, immunology, and pharmacology, and specifically funds to attack AIDS-associated diseases. Finally, we have to realize that, while it is appropriate for the lion's share of funds to be spent on designer drugs, we have a very large group of patients who don't have the time to wait for the designer drugs to arrive, and that consequently, we must mandate that a certain percentage of the funds appropriated in the name of the American people by this Congress will be targeted to investigating community-developed drugs, to see if they are in fact efficacious, so that I as a practicing physician can tell my patients that these drugs appear to hold promise and you should consider using them, while these drugs have no promise and they will be harmful or useless to your condition.

I would like to end by pointing out that we need management, and we need leadership, both of which have been woefully lacking. Congress mandated that the President appoint a commission to review the problem and produce specific recommendations for the United States' response to AIDS. We are hopeful that the President will move quickly. If he does not, Congress may well have to mandate that these recommendations be implemented.

Senator STAFFORD. Thank you very much, Dr. Conant.

I was not able to be here, Dr. Young, when you were testifying, but in light of the testimony that has been adduced recently, could your office advise us, within 7 days, of where the pentamidine is in the approval process?

Dr. YOUNG. If you would like, I can do that now.

Senator STAFFORD. You may do that now, Doctor.

Dr. YOUNG. In addition to the NIH studies, there are studies that have been done in private industry. None of those have been submitted as a treatment IND, and none of those have been filed yet for an NDA. They are between Phase II and Phase III. I said before Mr. Weiss, that if I were able even to write a treatment IND for it myself, I would do so.

I do not have that authority. I am looking forward to receiving an application in the not too distant future.

With regard to dextran sulfate, about which a question was raised, I would say that though the NIH trial has not enrolled many people, there is a trial that is in the private sector that has 36 people enrolled, and the studies are underway. And as I said earlier, we ourselves are trying to look and see whether that drug is absorbed, and what the pharmacokinetic levels are.

We do rely, Senator, on the data being presented to us, but, as I assured Senator Kennedy, this is not business as usual within the agency. I think the tragedy is that, as Dr. Gingell and others have said, they are looking for some degree of effectiveness. I am looking for some degree of effectiveness, too, and the choice is between whether to bring drugs out that have no effectiveness, which is possible for Dr. Conant—no effectiveness at all—or to look for drugs with effectiveness.

When the very great controversy came over the treatment IND recommendation, and a change was made to require demonstration of a modicum of effectiveness; now there is an outcry that there is too much effectiveness information required.

We will continue to keep you informed. I will provide for the record more detail, but I did want to comment directly that pentamidine is in Phase III; other Phase I studies are ongoing in the private sector.

[The information of Dr. Young follows:]

Two companies have active INDs for the study of aerosolized pentamidine; the INDs were filed July 17, 1987 and September 2, 1987. The National Institutes of Health through the National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Trials Group, also has an active IND for this drug which was filed on March 3, 1988. Two of the INDs are for studying both treatment and prophylaxis of Pneumocystis carinii pneumonia (PCP) while the other is for studying only PCP prophylaxis.

Aerosolized pentamidine was first studied in humans at the Memorial Sloan-Kettering Cancer Center outside of the IND mechanism; the marketed injectable form was administered by aerosol through commercially available nebulizers.

When the sponsors began to consider controlled trials to study PCP prophylaxis, this form of treatment had become so popular in the United States due to the availability of the intravenous form of the drug that placebo-controlled trials could not be performed. For this reason, many of the current trials are dose-comparison studies as the optimal dose of aerosolized pentamidine for PCP prophylaxis is presently not known. The controlled trials for treatment of PCP randomize patients to treatment with either aerosolized pentamidine or one of the two approved therapies for this disease (oral and intravenous trimethoprim/sulfamethoxazole or intravenous pentamidine).

In March 1988, the Opportunistic Infection committee of the NIAID's AIDS Clinical Trials Group recommended use of aerosolized pentamidine for prophylaxis of PCP in all AIDS patients who had recovered from an episode of acute Pneumocystis carinii pneumonia. The milligram amounts, nebulizer, frequency and duration of drug administration were not specified. FDA was asked for their opinion following this recommendation; we stated that we would be happy to review and evaluate the data on which this recommendation was based.

We are continuing to work with both sponsors to facilitate the licensing and availability of this product.

WPMAIL -ECHO
MAIL IMPORT-ALERT 'PILOT GUIDANCE FOR RELEASE'

DATE: JULY 20, 1988

FROM: DIRECTOR, OFFICE OF REGIONAL OPERATIONS (HFC-100)

SUBJ: "PILOT GUIDANCE FOR RELEASE OF MAIL IMPORTATIONS"

TO : REGIONAL FOOD AND DRUG DIRECTORS
DISTRICT DIRECTORS
IMPORT PROGRAM MANAGERS
COMPLIANCE BRANCH DIRECTORS
INVESTIGATIONS BRANCH DIRECTORS
LABORATORY BRANCH DIRECTORS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)

RICHARD SWANSON (HFC-160)
CHARLES EVERLINE (HFC-210)
ARTHUR LEVINE (GCF-1)
HOWARD PIPPIN (HFF-310)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
JACK HARTY (HFY-50)
BRUCE WILLIAMS (HPB-CANADA)
STERR LARSON (HFC-41)
SAMMIE YOUNG (HFD-301)

OFFICE OF ENFORCEMENT (HFC-200)
ERNEST BRISSON (HFC-230)
EDWARD STEELE (HFF-25)
OFFICE OF COMPLIANCE (HFF-300)
DANIEL MICHELS (HFD-300)
EDWARD BALLITCH (HFV-230)
WALTER GUNDAKER (HFZ-300)
WILLIAM B. CARTER (HFF-26)
BETTY CHISM (HFC-42)
THOMAS BOZZO (HFB-100)

******CORRECTED COPY******

NOTE: THIS GUIDANCE IS BEING ISSUED ON A PILOT BASIS AND IS SUBJECT TO CHANGE AND/OR CANCELLATION. IF THE PILOT PROVES SUCCESSFUL, WITH NO SIGNIFICANT PROBLEMS, CHAPTER 9-71 OF THE REGULATORY PROCEDURES MANUAL MAY BE APPROPRIATELY REVISED.

SUBJ: Pilot Guidance for Release of Mail Importations

Because of the desire to acquire articles for treatment of serious and life-threatening conditions like AIDS and cancer, individuals have been purchasing unapproved products from foreign sources. Some of these products

are sold over-the-counter in the country of origin while others are available from clinics where the purchaser was treated. Such products are often shipped to the purchaser by mail.

Even though such products are subject to refusal, we may use our discretion to examine the background, risk, and purpose of these products before making a final decision. To assure that the districts are operating in a uniform manner, the following guidance is provided for dealing with personal use shipments.

1. Except as modified by these instructions, established guidance found in RPM-9-71, exhibits X9-71-1 and X9-71-2 should be followed.

2. A product entered for personal use, which meets the criteria in item 4 below, may proceed without sampling or detention.

3. Products that are not identified, or are not accompanied by documentation of intended use, should be detained. Other reasons for detention may include: size of the shipment (amount inconsistent with personal use), fraudulent promotion or misrepresentation, or an unreasonable health risk due to either toxicity or possible contamination. In such cases, the appropppriate center should be contacted for guidance concerning release of the product.

4. Following detention, shipments may be released to an individual if the following criteria can be satisfied and there is no safety risk or evidence of fraud:

   - o the product was purchased for personal use
   - o the product is not for commercial distribution and the amount of product is not excessive (i.e., 3 months supply of a drug)
   - o the intended use of the product is appropiately identified
   - o the patient seeking to import the product affirms in writing that it is for the patient's own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product

5. If the district should encounter a situation suggesting promotional and/or commercial activity that falls within our health fraud guideline, the district should recommend that an Import Alert be issued for the automatic detention of the product and identification of the promoter involved.

6. The model letter currently in Exhibit X9-71-2 should be revised according to the attached during this pilot.

7. The article may then be RELEASED WITH COMMENT upon receipt of the letter as follows:

"The drug you have obtained for your personal use appears to be unapproved in the U.S. We understand you will use this limited quantity under medical supervision; however, future personal shipments may be refused entry if we learn, among other things, the drug presents an unreasonable risk or it has been commercially promoted to U.S. citizens."

The above guidance should be used as part of the current outstanding instructions for dealing with mail packages as found in Chapter 9-71 of the RPM.

/s/
Ronald G. Chesemore

See Pilot Guidance 7-20-88

MAIL IMPORTATIONS

9-71-00 Purpose
10 Background
20 Objectives
30 Guidance
40 Processing Procedures for Mail Importations

9-71-00 PURPOSE

To provide general guidance for the coverage of imports entered through the mails so as to provide the greatest degree of public protection within allotted resources.

9-71-10 BACKGROUND

We know that it is easy to spend much time and effort covering mail importations just as it is covering importations in personal baggage. However, again as with imports in personal baggage, coverage of mail importations results in little consumer protection because the transactions are personal and are small, both in size and value. We must remember the consumer protection provided by unlimited, extensive coverage of mail imports is not commensurate with the resources that are expended.

Some districts appear to be expending relatively more resources than others on the coverage of mail importations. This type of program can be ineffective in terms of the best consumer protection that can be provided.

9-71-20 OBJECTIVES

A. To adjust the attention given coverage of mail importations.

B. To provide a balanced and uniform approach for the coverage of mail imports.

C. To provide the greatest degree of public protection within allotted resources.

D. To affirm FDA's policy regarding the coverage of mail importations.

9-71-30 GUIDANCE

Generally, little time should be spent on the coverage of mail importations. Articles entering through the mails should not be detained except for the following substantial reasons:

A. When the size of the package(s) (lot) or the number of entries from a particular shipper or to a specific addressee in a given time period indicates the merchandise may be for commercial instead of personal use.

B. Importations (articles) which present an imminent danger to health.

C. When an "Import Alert" has been issued concerning a specific commodity.

D. When importations (articles), brought to our attention, are clearly actionable such as new drugs that are not covered by an approved NDA.

9-71-40 PROCESSING PROCEDURES FOR MAIL IMPORTATIONS

Generally, the procedure for handling mail importations should be the following:

-- Parcels should be opened and examined by the Customs Mail Division. Those believed to be subject to one or more of the criteria above should be set aside for examination by FDA.

-- Complete the Form FD-725 "Mail Collection Report" for each parcel selected for sampling. Generally a physical sample is not required on mail importations because a documentary sample e.g., labels, inserts, etc., will be sufficient for most label violations. However if a physical sample is needed collect only the amount needed for analysis by the laboratory from the mail parcel. The remaining portion should not be removed from the custody of the U.S. Customs Mail Division.

-- Violative mail importations detained according to the above listed criteria should be held by U. S. Customs in the mail room until either released or refused entry.

— Attached as guides are two specimen letters that may be sent with the Notice of Detention and Hearing when a parcel is detained.

Exhibit X9-71-1 - for use in general mail importations.

Exhibit X9-71-2 - for use in prescription drug mail importations

— Articles not subject to the FD&C Act but are contained with items subject to the Act should be listed on the mail collection report in the event of any question regarding the contents of the parcel at a later date.

— If the consignee submits a request for the release of those items not subject to FDA jurisdiction in a detained mail importation, and the request is accompanied with a statement permitting destruction of the violative article, the request with the statement and a Notice of Refusal of Admission covering the violative article should be referred to the Mail Division of U. S. Customs having custody of the parcel so they can determine final disposition of all merchandise, including destruction of the violative portion.

Model Letter for Use in General Mail Importations Exhibit X9-71-1

(LETTERHEAD)

A mail shipment of an article from a foreign country addressed to you is being detained at the post office. All products of this kind must meet the requirements of the Federal, Food, Drug, and Cosmetic Act or the other Acts enforced by FDA. These laws are designed to protect you from unsafe or misrepresented foods, drugs, cosmetics, devices, and other articles. Examination indicates the product addressed to you does not comply with the law.

Please read the enclosed Notice of Detention and Hearing carefully since it explains why the product is believed to be in violation. The Notice does not in any manner accuse you of violating any law.

If you have good reason to believe the product does comply with the law and wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice.

If you do not wish to do this, you may disregard the Notice.

The product will be returned to the sender without cost to you if we do not hear from you within the time stated.

Sincerely yours,

Enclosure:

Model Letter for Use in Prescription Drug Mail Exhibit X9-71-2

(LETTERHEAD)

A mail shipment of a drug from a foreign country addressed to you is being detained at the post office. All products of this kind must meet the requirements of the Federal Food, Drug, and Cosmetic Act, which is designed to protect you from unsafe or misrepresented foods, drugs, cosmetics and devices. Examination indicates that the product does not comply with the law.

Please read the enclosed Notice of Detention and Hearing carefully, since it explains why the product is believed to be in violation. The Notice does not in any manner accuse you of violating any law.

If this drug is not an investigational or new drug and you are taking it under the supervision of a physician, it may be released for your use provided you furnish the following:

1. A written statement from your physician (licensed by law to practice medicine in the United States), requesting that the drug be delivered to him for your use under his supervision.

2. A written statement from you, addressed to the post office authorizing them to readdress the package to your physician (Give his name and office address).

Send both statements to this office, and we will make arrangements promptly for release of the product.

If you have good reason to believe the product does comply with the law and wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice. If you do not wish to do this, you may disregard the Notice.

The product will be returned to the sender without cost to you if we do not hear from you within the time stated.

Sincerely yours,

Enclosure

77-1 (04/01/77)

Senator STAFFORD. Thank you very much, Doctor.

For the other members of the committee who are not able to be here at the present time, and the chairman, and myself, let me express our gratitude to all three of you, and it occurs to me that personally I will have some questions that I would like, in view of the time constraints, to submit to you in writing, if that would be agreeable, for a response at your earliest convenience. And I believe other members of the committee may also have questions that they might like to submit in writing.

So, again, expressing my gratitude to all of you, and the other witnesses who may still be in the room, for being with us this morning on this crucial issue of HIV and what to do about it, I say thanks and the meeting will stand adjourned.

[Whereupon, at 12:22 p.m., the Committee was adjourned, subject to the call of the Chair.]

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89-340 (204)